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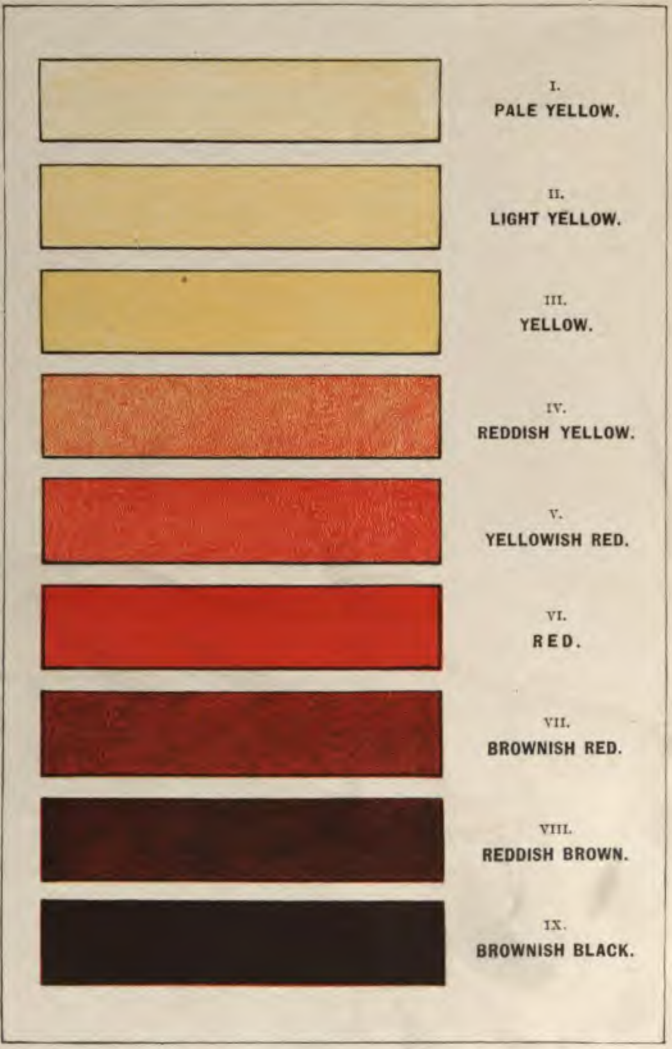

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S27
1904

TO

THE MEMORY OF

My Father

IN WHOSE LABORATORY I GAINED MY FIRST KNOWLEDGE OF
EXPERIMENTAL SCIENCE

THIS BOOK IS DEDICATED

PREFACE.

The object of this manual is to furnish a concise guide to the examination of urine for the practitioner in his daily work and for the student in his laboratory course, as well as in his study for examinations.

In accordance with this aim, an effort has been made to treat the important and practical parts of the subject as fully as possible, while theory, discussion of moot-points, and cumbersome analytic details have been either omitted or treated in the briefest possible manner.

The theory of urinary secretion and the methods of functional examination of the kidneys have been given a rather more prominent place than has been done in other text-books, for the reason that a knowledge of these themes, while still of little practical use, adds materially to a grasp of the modern status of uranalysis and of the directions in which advances may be expected in this science.

Special attention has been paid to technics and to the interpretation of findings. In this connection some hints as to the methods of working that developed in my own experience have been inserted, which I trust may prove helpful to the beginner.

In a text-book of this scope, it is not necessary to mention in detail the authorities consulted, and this has not been done here, except in a few instances. I take occasion, however, to acknowledge my especial indebtedness for material to the works of Neubauer and Vogel, Hammarsten, Von Jaksch, Ogden, F. C. Wood, Simon, Purdy, Heitzmann, and Tyson, and to express my sincere thanks to Dr. Henry T. Brooks, Pathologist to the Postgraduate Hospital, for many valuable hints in the preparation of this book.

The metric system is used in the greater part of the book, but the old system of weights and measures has been retained in some places for the sake of convenience in working, and in order to keep intact the original formulas of certain authorities.

Unless otherwise specified, the reagents and solutions are supposed to correspond to the standard of the United States Pharmacopœia.

If this little volume will contribute towards a clearer and more precise understanding of the subject of uranalysis on the part of the student or practitioner, my task shall not have been fruitless.

G. A. DeS. S.

New York, *August*, 1904.

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EXAMINATION

OF

THE URINE

EXAMINATION OF THE URINE.

PART I.

GENERAL CONSIDERATIONS.

CHAPTER I.

THE URINE AS A SECRETION.

A knowledge of the characters of the urine in health and disease is of the greatest importance to the physician, inasmuch as this fluid constitutes one of the most valuable aids to the diagnosis of disease, both medical and surgical. Next to the pulse and the temperature, the urine offers the greatest possibility for an insight into the workings of the human system. Aside from its purely clinical value, uranalysis is essential to the study of the physiologic processes of the body and the determination of changes in its metabolism produced through normal or abnormal influences.

The urine is a watery fluid secreted by the kidneys, and in health contains a large variety of constituents which are derived from the wasting and decomposition of the fluids and tissues of the body, and from certain elements of the food.

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EXAMINATION

OF

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filtrate from the tufts. These conditions—a thin, watery fluid on one side of a membrane (the tubular wall) and a thickened blood on the other side—are the ideal conditions for osmosis, and so an interchange of elements occurs in the kidney, whereby water from the urinary tubules passes into the blood, while the products of tissue waste—urea and salts—pass from the blood into the tubules, where they mix with the watery fluid and so form the urine. The second theory is that of Bowman-Heidenhain. According to this theory, the kidney is essentially a *secreting gland* and the urine is a mixture of certain characteristic elements, such as urea, etc., which are secreted by the epithelial cells of the urinary tubules, and of water and inorganic salts, such as sodium chlorid, which are filtered through the glomeruli from the blood. According to Bowman, therefore, the *glomeruli are filters* which send water and salts into the urine, while the *tubules are true secretory structures.* This theory has been confirmed by certain interesting experiments by Heidenhain, who injected methylene-blue into the blood of an animal and found soon afterward that the blue color appeared in the urine, and that epithelium of the tubules was stained blue, while the glomeruli were free from stain, thus showing that the tubular epithelium possesses selective powers like those of a secreting gland. The most important proof of the Bowman-Heidenhain theory, however, is the fact that when the epithelium of the tubules is destroyed by disease, urea and certain toxic products (?) are retained in the blood, producing uremia, while the urine is more watery and contains a smaller percentage of its characteristic solids.

Korányi, of Budapest, to whom we shall refer later (chapter XXIII: The Functional Condition of the Kidneys), has combined the theories of Ludwig and of Heidenhain. He admits, with Heidenhain, that water and salts are filtered through the glomeruli, while the other constituents of urine are secreted by the tubular epithelium, but he believes that there is a *perfect balance* maintained between the number of molecules of urea and allied products secreted by the epithelium of the tubules, on the one hand, and the number of molecules of sodium chlorid and other salts filtered into the lumen of the tubules through the glomeruli, on the other. The epithelium of the tubules, therefore, acts not only as a secreting cell with special properties, but also as a living membrane, through which osmosis constantly takes place from the blood into the tubule, and vice versâ, so that for every molecule of urea, etc., that passes from the blood into the tubule there is reabsorbed a molecule of sodium chlorid or other salts through this living membrane of epithelium into the blood. For this reason any changes in the epithelium wrought by disease will be reflected in changes in the proportion between the urea and the salts, as we shall see further on, in considering The Functional Condition of the Kidneys.

CHAPTER II.

SELECTION OF A SPECIMEN OF URINE.

For accurate quantitative work it is absolutely necessary to obtain the total amount of urine passed in twenty-four hours, or, at least, a sample obtained after mixing thoroughly the entire quantity so collected. In the latter case, the quantity eliminated in twenty-four hours must be measured and made known to the examiner. A perfectly clean bottle, holding about a half-gallon, should be used for collecting the twenty-four hours' quantity. It should be well corked after each addition, and should be kept in a cool, dry room to avoid decomposition. It is important that no foreign matter whatever, such as dust, feces, sputum, etc., be introduced into the sample, and the urine should never be allowed to stand in open or dirty vessels.

The reason for collecting the **twenty-four hours' quantity** is that the proportion of the constituents and the amount of albumin, etc., vary a good deal at different hours of the day and night, and that the object should be to obtain the average composition of the urine in the twenty-four hours.

The **best time** to obtain a sample of urine when we do not want the twenty-four hours' quantity, but merely wish to test qualitatively for sugar, albumin, etc., is during the day, about three hours after a meal. It is a mistake to take the morning urine, as is so commonly done, for in slight albuminuria the urine passed in the morning is the least likely to contain albumin, and the same is true of sugar in glycosuria. Sometimes, when a case requires careful study, a comparison of the day urine and the night urine is desired; in that case we collect the urine from 7 a. m. to 7 p. m. in one bottle, and from 7 p. m. to 7 a. m. in another bottle, each being appropriately marked.

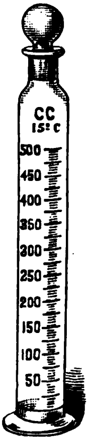

Fig. 1.—Stoppered graduate.

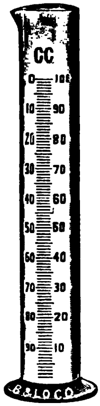

Fig. 2.—Cylindric graduate.

If a more concentrated urine is desired than is obtained in a given case with ordinary diet, it may be advisable to reduce the amount of water and other fluids ingested for a day or so, and thus a urine with greater concentration and more abundant sediment may be obtained for microscopic examination.

The urine is subject to rapid **decomposition** after being voided, as the result of the action of molds and other micro-organisms, and also as the result of reactions between its various constituents. On standing, a normal urine precipitates, as a rule, first, some amorphous urates, then some uric-acid crystals, and sometimes calcium oxalate. If allowed to stand open, and if exposed to high temperature, as in hot weather, the urine becomes clouded from the large number of bacteria and fungi. At the end of a few days it becomes ammoniacal—that is, the urea is gradually transformed into ammonium carbonate, according to the following formula:

$$CH_4N_2O + 2H_2O = (NH_4)_2CO_3.$$

In consequence of this the urine grows alkaline and the sediment contains ammonium urate, triple phosphate, and amorphous masses of calcium phosphate. Urines of normal concentration and acidity do not decompose so rapidly as urines of low density and slight acidity.

While this series of changes is known as *alkaline fermentation*, there is another form that has been known as *acid fermentation.* It consists of an increase in acidity, a darkening in color, and the deposition of uric acid and urates, and occasionally of calcium-oxalate crystals, together with many yeast fungi and bacteria. This change is probably caused by the mucus, which acts as a ferment and induces an acetic-acid or lactic-acid fermentation.

Preservation.—It is very important, therefore, that the urine be examined in as fresh a state as possible. In order to preserve it during the collection of the specimen or during the transportation to the laboratory, etc., a number of substances have been used as antiseptics. The most practical is the addition of a crystal or two of thymol, or an ounce of cold saturated solution of boric acid to the quart of urine. The use of formalin, of which two or three drops are added to the urine, has been advocated of late, but it is apt to cause a peculiar precipitate supposed to consist of formalin and urea, and, besides, is apt to affect the organized sediment, shrinking the cells and distorting the casts. The addition of formalin to urine also obscured the microscopic examination, in the author's experience, by the production of innumerable gas-bubbles if the urine was allowed to stand for any length of time. The addition of 5 grains of salicylic acid to 4 ounces of urine is favored by some, and is said to be very efficient.

QUESTIONS ON CHAPTERS I. AND II.

Name the principal groups of constituents in the normal urine.

What gases are found in it?

What inorganic salts? What organic substances?

How many theories of urinary secretion are there at present? By what names are they known?

What is Ludwig's theory, in your own words?

On what physical principles does Ludwig's theory of secretion depend?

What is Bowman-Heidenhain's theory?

How does Bowman regard the kidney essentially?

What part of the urine is secreted by the tubular epithelium? What part filtered by the glomeruli?

Mention experiments to confirm this theory.

What is the most important pathologic proof of this theory?

What is Korányi's teaching as regards the number of molecules of urea, etc., secreted, and of sodium chlorid, etc., filtered?

Give the rules in selecting a specimen of urine.

How is the specimen collected?

Why do we insist upon the twenty-four hours' quantity?

At what time should urine be taken if it is not possible to obtain the twenty-four hours' quantity, and why?

Describe the processes of decomposition occurring in urine upon standing.

What constitutes alkaline fermentation?

What is known as acid fermentation?

How should urine be preserved from decomposition?

CHAPTER III.

PHYSICAL PROPERTIES OF THE URINE.

Amount.—The amount of urine passed during twenty-four hours by a healthy adult is from 1200 to 1600 c.c., the average being about 1500 c.c. or about 50 fluidounces. Women pass smaller quantities than men, and small-sized persons void less than large-sized individuals. The drinking of large quantities of liquids increases, while the taking of violent exercise, through free perspiration, diminishes, the average amount. In health the largest amount is usually passed in the afternoon, a moderate amount in the forenoon, and the smallest amount during the night.

In warm weather considerably smaller quantities are passed than during the cold months. In disease the quantity of urine may be diminished or increased, or the urine may be suppressed through obstruction, or retained in the bladder through an impediment in the region of its neck or in the urethra.

Oliguria is a term used for diminished quantity of urine. *Anuria* is used to designate cases in which no urine, or a very small quantity, is passed—*i. e.*, when there is a partial or complete *suppression* of urine. *Polyuria* is a term used for a markedly increased quantity of urine. *Hydruria* means an increased proportion of the watery constituents of the urine, the total quantity also being increased.

Diminution in quantity is noted in fevers; in shock after anesthesia or after operations on the genito-urinary organs; in stasis in the kidney due to heart disease, etc.; in acute congestion of the kidney; in acute nephritis and in the acute phases of chronic nephritis; in diseases accompanied by diarrhea and vomiting, such as cholera or yellow fever, and in all diseases in the last stages before death.

Increased quantity is observed in diabetes mellitus and insipidus, in some diseases of the nervous system, such as hysteria and convulsions, and in cerebral hemorrhage; in convalescence from acute and inflammatory diseases; in convalescence from acute congestion and from acute diffuse nephritis; in chronic nephritis, both interstitial and diffuse, and in amyloid kidney; in hypertrophy of the heart, and in all conditions causing increased blood-pressure; also in cases in which diuretics have been freely used or a large amount of water drunk.

With the exception of the chronic diffuse and interstitial varieties of nephritis, in which there is an increase, there is a tendency to diminution in all forms of Bright's disease. A marked diminution in the urine in chronic nephritis, if accompanied by low specific gravity, is a very grave sign and usually precedes death.

Color.—The normal color of urine is of a pale yellow, straw, or amber tint, but even in health it may vary considerably according to the amount of water drunk, etc. Dilute urines are usually pale; concentrated urines are deeply colored. The action of the skin in perspiration, the quantity of water drunk, and sometimes the quality of the food may have to do with changing the color of the urine in health. Color is not a very trustworthy sign in urine examinations.

In disease the color of urine may be changed, owing to the increase or diminution of the normal coloring-matters or the addition of abnormal pigments. The general rule stated before about the proportion of color to concentration usually holds good in disease. *Very pale-colored* urine occurs in diabetes insipidus, hysteria, interstitial nephritis, etc. *Highly colored urine* occurs in acute fevers and in inflammations, and is due to concentration and also to the presence of uroerythrin. (See p. 169.) *Reddish urine* is always due to the presence of abnormal coloring-matters, usually blood. A *brown* or *reddish* color is seen in urines after ingestion of rhubarb and senna; a *yellow* color, after santonin. A *dark-brown* urine may be a sign of hemorrhage from the kidney, and be due to the presence of methemoglobin or hematin. *Smoky and dark urine* is often seen after carbolic acid has been used internally or sometimes after its external use, as well as after the taking of large doses of salol or guaiacol. These urines show the black color especially on standing, owing to the formation of hydroquinon as the result of decomposition of the phenol. (See Phenol, p. 162.) A dark urine is also seen in the presence of alcapton. (See p. 118.)

Bile-pigments, when present in excess, give a dark color with a yellowish-green foam, and on standing the urine become *greenish*. In cholera and typhus the urine may be *blue*. In melanotic cancer the urine is almost *black*, especially after standing, owing to the presence of melanin. A *greenish-blue* urine is eliminated after methylene-blue has been taken. A greenish tint is also sometimes seen after the use of a large quantity of milk, also in chronic Bright's disease and in diabetes with large amounts of sugar.

Odor.—The odor of normal urine is peculiar, aromatic, sometimes styled "urinous." It is due to the presence of volatile acids—phenylic, taurylic, and damaluric—in very minute quantities, and partly also to urea. The odor is strongest in concentrated urine. On standing, normal urine acquires a disagreeable odor which is both putrid and ammoniacal. The putrid odor is due to decomposition of mucus or other organic matters. The ammoniacal odor is due to the formation of ammonium carbonate. It is important to note the odor of *freshly passed urine*, for if it is putrid or ammoniacal, the urine must have decomposed within the body—*e. g.*, in the bladder. A urine which contains a large amount of pus or albumin may suffer decomposition of its proteid matter to such an extent as to evolve an odor of sulphureted hydrogen. A fecal odor is noted when there is contamination of the urine by the feces through a fistula, etc.

Certain *vegetable foods* and *certain drugs* when taken internally very quickly produce a peculiar odor in the urine. Thus turpentine produces the odor of violets; cubebs, copaiba, sandalwood oil, asparagus, etc., produce their characteristic odors in the urine.

In disease the only abnormal odors to be noted are the increased odor, usually styled "strong," in concentrated urine; the sweet or fruity smell of diabetic urine; the foul odor of cystitis, and the "sulphureted" odor of urine containing much pus. A peculiar odor, intense in its foulness, is noted in pyelitis. A sulphureted odor is noted in the presence of cystin in decomposing urines containing this substance.

Consistence.—Normal urine is always of the consistence of water. When the urine contains much pus or mucus, especially if it has become alkaline, it becomes very thick and stringy. Urine containing much sugar or albumin tends to froth when shaken. Chylous urine which contains fat in fine emulsion is thickened in consistence.

Transparency.—Normal freshly voided urine is always perfectly clear, but on standing a few minutes there is generally a faint cloud which floats usually in the center of the urine or settles at the bottom if the urine is dilute enough. This cloud or "*nubecula*" consists of mucus, epithelium, bacteria, and débris of cells. It is much more pronounced in women, on account of the admixture of vaginal mucus, which becomes washed away from the genitals in the passage of the urine from the urethra. In catarrhal conditions of the genito-urinary tract, especially in cystitis, prostatitis, and urethritis, the normal mucous cloud is markedly increased, so that the urine appears cloudy soon after being voided, and that the cloud sinks more rapidly to the bottom. The mucous cloud may be distinguished from other causes of turbidity by the fact that it tends to float in the center of the fluid, and is precipitated on the addition of an excess of acetic acid.

A cloudy urine may be the result of the presence of bacteria, phosphates, urates, or pus.

Bacteria, when present in large numbers (bacteriuria), give rise to a faint cloud which tends to float in the middle of the vessel and does not settle, even when the urine stands for a long time. This cloud, unlike the mucous cloud, remains unchanged on the addition of acetic acid.

Phosphates may give rise to cloudiness when there is an excess of the earthy or triple salts and when the acidity of the urine is lowered, thus lessening the solubility of the phosphatic elements. It is difficult to mistake turbidity due to phosphates for anything else, as it does not form a cloud, but pervades the urine uniformly, settling slowly on standing. A few drops of acetic acid, by correcting the lowered acidity, will almost instantly clear up the urine in such cases.*

Urates, if present in excess in normal acid urines, may cause turbidity or may give a sediment of urates—of sodium, potassium, calcium, and magnesium—if the urine be allowed to stand in the cold. This deposit settles quickly, is white, pinkish, dirty-yellow, or brick red in color, and often settles on the sides of the vessel. It is well to remember that a sediment occurring in acid urine can be composed only of urates or of organized elements (pus-cells, casts, etc.). The distinguishing test for the cloudiness due to urates consists in heating the urine gently over the flame, which quickly dispels the cloudiness and clears the urine.

---

* With a deposit of phosphates there usually is a certain amount of carbonates which add to the cloudiness. They are also dissolved on the addition of acetic acid.

Pus in the urine shows its presence by cloudiness immediately after passing, and on standing a few minutes by the deposit of an opaque, amorphous, yellowish-white sediment, which sinks to the bottom much more rapidly than mucus. In the presence of an admixture of pus and mucus the opacity of the sediment and the rapidity of its sinking grow less as the mucus is increased. In an alkaline or ammoniacal urine the pus-deposit occurs as a tenacious, gelatinous-looking mass which adheres to the bottom and to the sides of the vessel. On repeatedly shaking the urine, it is impossible to disintegrate this mass completely, and if it be allowed to settle and the urine be then decanted into another vessel, the gelatinous pus is often dislodged in a lump and precipitated into the second vessel.

To test a cloudy urine for pus, as distinguished from mucus, urates, etc., *Donné's reaction* is of value. It consists of allowing the sediment to settle in a conic glass, decanting the urine which floats over it, and adding a solution of potassium hydrate drop by drop until the gelatinous, glairy mass described above is formed, adheres to the bottom of the vessel, and slips out from it in a lump. This same mass is formed naturally in purulent urine on alkaline fermentation. The same test may be performed more rapidly by adding equal parts of the KOH solution to the urine and observing the appearance of the gelatinous precipitate.

A good rule, given by Tyson, is that if such a gelatinous mass is found, on standing, in alkaline urine, and if we are not clinically sure that we have pus and not merely mucus, another specimen of the urine, acid in reaction, should be obtained. If, then, the urine still shows a similar glairy mass, it may be safely assumed to be mucus.

The table on p. 35 shows in a condensed form how the source of turbidity may be detected in a few seconds in a urine with the use of only two reagents and heat.

Chyluria may be mistaken for pyuria. The former depends upon the presence of a parasite—Filaria sanguinis hominis—in the blood, and is characterized by urine which is a fat-emulsion and is milky in appearance. This urine will stand for days without settling, is milky, yellowish-white in color, and shows a film of fat or of creamy flakes on the surface. The fat is dissolved on shaking with ether and the urine is cleared. When there is much fat, chylous urine may coagulate on standing.

Reaction.—The reaction of normal urine is faintly

DIFFERENTIATION OF THE PRINCIPAL CAUSES OF TURBIDITY IN URINE.

I. *Heat the urine for a few seconds:*

A. *Turbidity increases or precipitate forms:*
= Bacteria, mucus, phosphates, or pus.*

Turbidity disappears:
= Urates.

II. *Add acetic acid:*

Turbidity unchanged:
= Bacteria.

Increased, or precipitate:
= Mucus or pus or both.

Dispelled at once:
= Phosphates.

III. *Add potassium hydrate:*
Turbidity or precipitate is changed to gelatinous coagulum:
= Pus.

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* If the turbid urine contains albumin, the precipitate will increase with heat and with acetic acid, but will disappear on the addition of an excess of alkali (soluble alkali albumin). Albumin is omitted from this table because in itself it does not cause turbidity in urine.

acid to blue litmus-paper; but occasionally it is faintly alkaline to red litmus and faintly acid to blue litmus—in other words, amphoteric. The mixed quantity of twenty-four hours is always acid normally. The acidity is due to the presence of acid sodium phosphate (monosodic acid phosphate — NaH_2PO_4) and not to free acid. This sodium phosphate is derived from the basic or disodic phosphate, Na_2HPO_4, neutral or alkaline in reaction, which combines in the blood with uric acid according to the following reaction, which takes up part of the sodium and leaves an acid salt:

$$Na_2HPO_4 + H_2C_5H_2N_4O_3 = NaH_2PO_4 + NaHC_5H_2N_4O_3.$$

The acidity of the urine depends upon the amount of the acid phosphate as compared with that of the disodium or alkaline phosphate. The urine is neutral or amphoteric when the disodium salt is present in a larger quantity, although not enough to neutralize the monosodium or acid salt, so that both blue and red litmus-papers give a reaction (Huppert).

Normally the acidity of the urine *varies at different times of the day*, there being an ebb and flow of the acidity tide corresponding with the meals. The acidity begins to diminish soon after a meal, and reaches its lowest point in about three or four hours, the urine even becoming alkaline at such times. The urine is less acid after a vegetable *diet*, and is increased in acidity after a red-meat diet. The *discharge of hydrochloric acid* by vomiting, washing out the stomach, or through a fistula, or the presence of an excess of hydrochloric acid in the stomach may cause an alkaline reaction. The urine may become alkaline after *hot baths* and free *perspiration. Alkaline salts* or *vegetable acids* given internally or taken in the food will increase the alkalinity of the urine, as the acids are converted into carbonates in the blood, pass into the urine as such, and render it alkaline. Freshly passed urine may be alkaline from conditions described above,—that is, from changes in the blood,—or it may be alkaline from *decomposition* or stagnation *in some part of the urinary tract.* In the former case the urine contains *fixed* alkali (sodium phosphate, etc.); in the latter case, *volatile* alkali (ammonia). The difference may be discerned by the odor and also by the fact that if the alkalinity is due to fixed alkali, the litmus-paper retains its blue color on drying, and if to volatile alkali, the paper on drying returns to red.

The changes in reaction due to decomposition on standing have already been considered under the heading of Selection of Specimens. In testing the reaction of urine strips of litmus-paper are used—the blue paper turns red in acid urines; the red paper turns blue in alkaline urine, and if the urine be amphoteric, both reactions take place. In testing, the paper should be dipped to about half its length into the urine.

Specific Gravity.—The specific gravity of normal urine is between 1012 and 1024 when the amount passed is normal. The standard normal average is 1020 at 60° F. (15.5° C.). In disease it varies between

1002 and 1060. It is proportionate to the amount of total solids in the urine, and these in turn vary according to the time of the day, the meals, the amount of exercise, the amount of fluid drunk, and the total amount of urine passed daily. A scientific determination of specific gravity cannot be made, therefore, without a specimen from the mixed twenty-four hours' quantity. Determinations with specimens obtained at various times may be necessary, but they are of no value unless the conditions of diet, exercise, temperature, etc., are known.

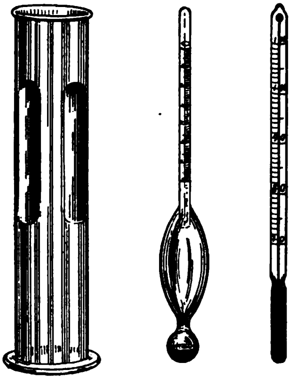

Fig. 3.—Squibb's urinometer with thermometer and cylinder.

Determination.—The specific gravity of urine is usually determined clinically by the use of a special hydrometer or *urinometer* (Fig. 3), which is sufficiently accurate for ordinary work. The best type is that of Squibb. The urinometer is constructed for a scale between 1000, which is marked at the top of the stem, to 1060, its principle being that the weight of the instrument is constant and that the denser the fluid, the less deeply will the instrument sink in it. A small cylinder holding about two ounces, sometimes made with flutings, intended to lessen the amount of urine required, is supplied with each instrument, with a thermometer showing the temperature of the fluid tested. Every urinometer must be tested with distilled water at 60° F. (15.5° C.), in which it should sink to 1000, or zero. (Squibb's urinometers are standardized at 22.5° C. or 77° F., a more convenient temperature for clinical work.) Carefully made urinometers have accurate division of the fractions of degrees, which gradually approach one another as they get nearer the bulb, as allowance is made for the weight of the stem above the water. The best instruments have been tested by the makers and bear the correction for variations in temperature on the container.

In determining the specific gravity a sufficient amount of urine is poured into the cylinder, which should not be too small in proportion to the urinometer, as the latter must not, on any account, be allowed to impinge against the side of the cylinder. If this occurs, the influences of friction and of capillary attraction tend to prevent the instrument from sinking. The urinometer should be dried before immersion. The foam should be removed from the urine by means of filter-paper, and the instrument should be lowered gently with a slight spinning turn, which will prevent it from being attracted to the sides of the vessel. The reading should be taken when the instrument is completely at rest and is not touching the sides of the cylinder at any point. The urine will be found rising in a small hillock around the stem (Fig. 4), over the level of the fluid, and in reading, care must be taken not to read at the top of the hillock, but at the level of the lower portion of the meniscus formed at the contact of the urine with the stem.

The specific gravity of urine should never be taken in a specimen freshly voided, as the latter is apt to be at or near the temperature of the body,—*i. e.*, 98.6° F. (37.2° C.),—while the urinometer is made for about 60° F. (15.5° C.). If an immediate examination is required, the specimen must be cooled rapidly to the proper temperature by immersing the cylinder in cold water. A correction for temperature may be roughly made with sufficient accuracy for clinical purposes by adding 0.001 to the specific gravity read for every 3° C. that the urine is below the point at which the urinometer is standardized, or subtracting the same amount for every 3° that the urine is above that point.

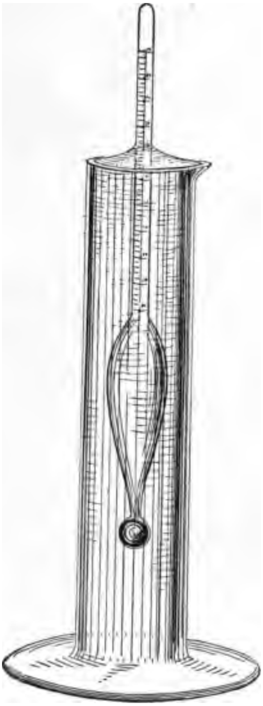

Fig. 4.—Urinometer immersed, showing effect on the surface of the urine.

Other and more accurate methods for estimating specific gravity are the Westphal-Mohr balance, the pyknometer, Sprengel's tubes, etc.

The *Westphal balance* is a beam-scale, finely constructed, which has a small glass thermometer suspended by a fine wire from the balance end in the urine to be tested. The weight of this thermometer in urine, as compared to its weight in distilled water at standard temperature, gives the specific gravity of the urine. These balances are very accurate, but their price is somewhat high and the urinometer is sufficiently accurate for the practising physician.

The methods for determining the specific gravity by means of the pyknometer, Sprengel's tubes, etc., may be found in text-books on physics. They require an accurate analytic scale, and depend upon the principle of comparing the weight of a very accurately measured volume of distilled water with exactly the same volume of urine of the same temperature, the specific gravity being deduced from the ratio of these two weights. They constitute the most accurate methods for taking specific gravity, but are useful only for strictly scientific work.

In taking the *specific gravity of small amounts of urine*—*i. e.*, amounts less than the 30 c.c. which are required to float a Squibb's urinometer—we are compelled to resort to some expedient other than the ordinary method. The use of *test-tubes* instead of cylinders is not to be countenanced, inasmuch as the readings cannot be accurate, the instrument constantly adhering to the wall of the tube by capillary attraction. The method of *diluting* the urine with water a certain number of times and multiplying the specific gravity of the diluted urine by that number is, if anything, still less accurate, for the error is multiplied in proportion to the dilution, and no urinometer is made accurate enough to read such exceedingly low gravities as are shown by diluted specimens. The use of the Westphal balance enables us to read the specific gravity of 15 or 20 c.c., and the pyknometers and Sprengel's tubes may be used with still smaller quantities, but all these are inaccessible to the physician on account of the high price of the apparatus they require.

A special method devised by the author for the estimation of specific gravity in the smallest amounts of urine without recourse to expensive appliances or complicated manipulation consists in the use of a *urinopyknometer*, which is a new form of hydrometer that determines with clinical accuracy the specific gravity of about 3 c.c. of urine. In this instrument the urine is placed in the hydrometer instead of the hydrometer being floated in the urine. The urinopyknometer is a little smaller than the ordinary urinometer, and consists of a small flask with a well-fitting glass stopper, the head of which bears a tiny bead of mercury (Fig. 5, *a*). This flask is attached to a small spheric bulb (Fig. 5, C), over which is the stem (A B) of the instrument, graduated in reverse order as compared to the ordinary urinometer—that is, the mark 1060 is at the top of the stem and the mark 1000 at the bottom. When the flask is filled with distilled water up to the mark M, and when the instrument is closed and immersed in distilled water, it reads 1000 at the level of the distilled water. When urine is poured into the flask to the same mark, the instrument sinks in distilled water in proportion to the specific gravity of that urine, which is then read on the scale. The same precautions in reading are taken in using this instrument as with the urinometer, and, in addition, the flask must be dry and perfectly clean (washed with alcohol or ether). The urine must be poured in accurately with a small dropper until it reaches the mark, so that the lower meniscus touches it as the flask is held at the level of the eye. At the time of writing the instrument has just been placed before the profession,* and has proved sufficiently accurate for clinical purposes. This instrument is of special value in cases in which very small amounts are furnished for analysis, as in infants, in catheterizing the ureters, and in emergency work.

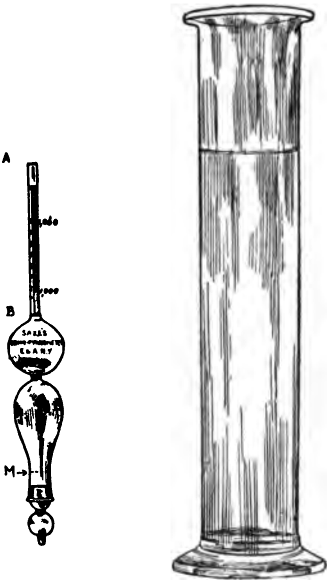

Fig. 5.—Urinopyknometer and jar for same.

Pathologic urines often show an increase or a diminution in specific gravity, but inasmuch as the latter varies normally to a considerable extent with the quality of meals, the amount of exercise, etc., an abnormal specific gravity is of value only when obtained from a twenty-four hours' specimen *the volume of which is known.*

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* "New York Med. Jour.," Oct. 17, 1903.

The specific gravity of urine is *increased* in the beginning of acute fever, after prolonged surgical operations, especially with ether anesthesia, on account of the hemorrhage and the perspiration; in acute Bright's disease in its early stages; and in other conditions accompanied by blood in the urine. In the presence of large amounts of sugar in diabetes the specific gravity may be very high and sometimes reaches 1050. When a large amount of urine is passed of a high specific gravity, we suspect diabetes, but absence of sugar must not be inferred from a low specific gravity.

A *diminished* specific gravity occurs in diabetes insipidus, in hysteria, and in chronic interstitial nephritis. In all forms of Bright's disease, except in the acute in its first stage, and in stasis in the kidneys of heart disease there is a tendency toward a lower specific gravity as well as a lessened percentage of urea. If no albumin and no sugar be present, the rule is that a lower specific gravity usually means less urea. A marked decrease in specific gravity is a serious symptom in chronic Bright's disease.

Total Solids.—The determination of the total solids eliminated in the urine during the twenty-four hours is useful clinically, inasmuch as it gives an insight into the relations of quantity and specific gravity. The general rule is that the quantity of urine is small when the specific gravity is high; in other words, that the specific gravity varies in proportion to the concentration—*i. e.*, in proportion to the amount of solids dissolved in the fluid. In certain diseases there is a noteworthy diminution of the total solids excreted, reflected in a lower specific gravity, and it is useful to know whether a lower specific gravity in a given case depends largely or materially upon an increased amount of the watery element of urine or upon a markedly decreased amount of total solids.

For clinical purposes, the amount of total solids in the twenty-four hours' urine is determined approximately by multiplying the last two figures of the specific gravity by *Haeser's coefficient*, which is 2.33, and thus obtaining roughly the number of grams of solids in 1000 c.c. (1 liter) of urine (33.8 oz.). This number, multiplied by the number of cubic centimeters passed in twenty-four hours and divided by 1000, will give the amount of solid constituents eliminated in twenty-four hours.

Example: The specific gravity of urine is 1020. Multiply the last two figures by 2.33: $20 \times 2.33 = 46.6$ grams in 1000 c.c. of urine; therefore, $\frac{46.6 \times 1500}{1000} = 69.9$ grams of solids in twenty-four hours.

This method is sufficiently accurate for clinical purposes, but for scientific work a given amount of urine is evaporated in a previously weighed porcelain dish, the residue dried, allowed to cool, and weighed repeatedly until there is no further loss of weight from drying. The variations between the solids found by weighing and those found by multiplying by 2.33 are, on the average, very slight. *The average excretion of solids* is 61.14 grams (945 gr.) in twenty-four hours for a person weighing 145 pounds avoirdupois (66 kilos). According to the weight of the person, this normal standard will have to be deducted from or added to. Parkes lays down the rule, which he worked out by means of the combined observation of a number of authors, that 10 per cent. must be deducted from the average solids in persons between forty and fifty years of age; 20 per cent. between fifty and sixty; 30 per cent. between sixty and seventy; and 50 per cent. above seventy. The normal standard applies to an ordinary diet of mixed foods and to the ordinary exercise of a healthy man in daily work. In persons who have fasted for two days or longer, as in fevers, etc., one-third should be deducted from the average solids; one-eighth if the diet be spare; one-tenth if somewhat below that of health. For perfect rest one-tenth should be deducted; for comparative rest, one-twentieth.

It should be noted that no deductions can be drawn as to the amount of *any particular solid* from the weight of the total solids, and especially that although urea normally constitutes about one-half of the solids excreted, an estimation of the urea present by dividing the amount of total solids by two is of no value, as the *proportions* of the various constituents vary markedly.

Total Acidity.—There is no way of rapidly estimating the total acidity of urine in clinical work, although this would be desirable in cases in which we suspect an increase of the acid constituents. Attempts to determine the acidity of urine by titration with an indicator have usually proved failures. The reaction of urine is chiefly produced by phosphates. As there is no phosphate which is neutral to litmus-paper (the acid phosphate gives an acid reaction while the normal or monoacid phosphate is alkaline), litmus cannot be used as an indicator in urine. The difficulty with other indicators is that it is impossible to watch accurately the end-reaction, on account of the color of the urine. Finally, according to Lieblein, there is still another source of error; namely, the fact that the addition of an alkaline solution, such as would have to be used in titrating, induces a combination between the calcium chlorid and the alkaline phosphate, resulting in the formation of a calcium phosphate of variable constitution, and that the phosphoric acid is, therefore, not neutralized in constant proportion. The amount of phosphoric acid which remains non-neutralized will depend upon the amount of earthy alkalis in the urine.

For these reasons the methods of acidimetry usually outlined in text-books on uranalysis are of no clinical value, and the best substitute is the determination of the total phosphoric acid contained in the diacid phosphate in the urine, which is given under the heading of Phosphates in a subsequent chapter. (See p. 201.) In this way we can get an exact numeric expression for the acidity of the urine.

The so-called **oxalic-acid method,** in which the total acidity is expressed "in terms of oxalic acid," is recommended by Purdy, but is not trustworthy, and has proved very unsatisfactory in the author's hands. It is as follows: Take 100 c.c. of urine from a twenty-four hours' specimen and titrate it in a flask or beaker with a decinormal solution of NaOH, using a sensitive litmus-paper as an indicator until a faintly alkaline reaction is produced. The number of cubic centimeters of the NaOH solution, multiplied by 0.0063, will give the percentage of acidity in terms of oxalic acid, the total acidity thus found corresponding to from 2 to 4 grams of oxalic acid a day.

QUESTIONS ON CHAPTER III.

Amount.—What is the normal amount of urine passed by an adult? What is the average? How does it vary according to the sex and size of the person? According to the amount of liquid drunk and the amount of exercise? According to the time of day in health? According to season?

Define oliguria; anuria; polyuria; hydruria.

When is diminution in quantity noted?

When is an increase noted? What is noted in Bright's disease, as a rule, as regards the quantity of urine?

Color.—What is the normal color of urine? On what does it depend in health? In disease? In what diseases do very pale urines occur? Highly colored urines? To what is a reddish urine due? A dark-brown urine? A "smoky" urine? A black urine? A yellowish-green foam? A blue urine? A greenish-blue urine?

Odor.—What is the odor of normal urine? What is it due to? What does an ammoniacal odor in a freshly passed urine indicate? An odor of sulphureted hydrogen? A fecal odor? An odor of violets? A drug odor? A fruity odor?

Consistence.—When does urine become thick and stringy? When does it tend to froth? What is the consistence of chylous urine?

Transparency.—Describe normal urine as regards transparency.

What is the nubecula? How is the nubecula noteworthy in women? When is it increased and how does the cloud behave then? How is this cloud distinguished from other causes of turbidity? What are these other causes? How does a cloud due to bacteria behave? A cloud due to phosphates? To urates? How are these clouds distinguished from one another? What is the behavior of cloudiness due to pus? What is Donné's reaction for pus? How is chylous urine distinguished? Give in tabular form the tests distinguishing all these causes of cloudiness.

Reaction.—What is the normal reaction of urine? What is it due to? When is urine neutral or amphoteric? How does its acidity vary normally? When is freshly passed urine alkaline? How do you test reaction in urine?

What is the normal *specific gravity* of urine? How does it vary and why? What is needed for accurate determinations? Describe the urinometer and its mode of application. What other methods may be used? What is the Westphal balance? Describe the urinopyknometer and its uses. What precautions should be taken in reading the specific gravity with any urinometer? When is the specific gravity of urine increased? When is it diminished? In what disease is a marked diminution of the specific gravity a grave symptom?

What is the clinical value of a knowledge of the *amount of total solids?* How is this amount calculated approximately? What is the average amount of solids excreted in twenty-four hours? What changes must be made in this figure to allow for age? for exercise and diet?

What is the best way to obtain an idea as to the *total acidity* of the urine? What do we mean by acidity "in terms of oxalic acid"?

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PART II.

CHEMIC EXAMINATION OF THE URINE.

A. ORGANIC CONSTITUENTS.

I. PROTEIDS.

CHAPTER IV.

ALBUMIN.

The most common proteid in the urine in disease is serum-albumin, although pathologic conditions of the kidneys, of the blood, or of other organs may also result in the excretion of other proteids, such as serum-globulin, fibrin, hemoglobin, albumose, peptone, nucleo-albumin, etc. By *albuminuria* we usually mean the presence of serum-albumin, without regard to the possibility and probability of the presence of other proteid constituents of minor importance.

It has been shown (Leube, Fürbringer, Senator, and Posner) that a healthy kidney may excrete a certain amount of albumin, although very careful experiments have proved that not every urine conins albumin (Leube and Winternitz). According to Grainger Stewart, the minute quantities of albumin in normal urines are due to epithelial and other débris. At any rate, there is no doubt that occasionally serum-albumin and serum-globulin in small quantities occur in the urine without any changes in the kidney, probably owing to a sudden disturbance of the circulation (von Jaksch). Recent studies by Ott and others have shown that nucleo-albumin is present in all healthy urines, and that, consequently, it is very important to distinguish this proteid from serum-albumin. (See Nucleo-albumin, p. 84.)

Albumin, like other proteids, is a colloid which does not crystallize and does not penetrate through animal membranes. So long as the animal membrane—in this case, the tubular epithelium—remains intact; so long as the proteid itself remains unchanged; so long as the pressure in the blood-current and in the excretory channel remains normal, no albumin is excreted by the kidney. (See Secretion of Urine, p. 19.) Albuminuria may be due, therefore, to one of three factors, namely: (1) Changes in the kidney which affect the excretory epithelium; (2) changes in the blood which render its serum-albumin more diffusible; (3) changes in the blood-pressure. Serum-albumin in noticeable amounts is never found in healthy urine, and its presence is always an important clinical symptom.

Albuminuria may be divided into that form derived from the kidney (renal albuminuria) and into that due to admixture of proteid exudates from other parts of the urinary passages (accidental albuminuria).

Accidental albuminuria may be disposed of in a few words. Pus, serum, and lymph are the sources of this admixture of proteids, and they may come from the pelvis of the kidney, the ureters, the bladder, or the urethra; from fistulas between the urinary tract and other parts, etc. The presence of pus-cells and the absence of casts and epithelium from the kidney are usually sufficient to distinguish these cases, in addition to their other clinical features and to the fact that very little serum-albumin is present while a larger quantity of the other proteids is found.

Renal albuminuria depends upon disease or disturbance in the kidney. The following classification of the conditions in which albuminuria occurs may prove of value:

1. *Nephritic Albuminuria:* Depends upon structural changes in the kidney, including all forms of Bright's disease.
2. *Circulatory Albuminuria:* Due to disturbances of circulation—Epileptic paroxysms; acute enteritis; renal congestion; emphysema; heart disease; fatigue; excessive muscular exercise; cold baths; vasomotor disturbances in nervous disease.
3. *Febrile Albuminuria:* Due to changes in the blood-pressure; to alterations in the kidney produced by micro-organisms or their toxins.
4. *Hematogenous Albuminuria:* Occurs independently of kidney disease, of disordered circulation, and of fevers, in anemic and cachectic persons (von Bamberger).
5. *Intermittent Albuminuria:*
    - (*a*) In health: Pavy's cyclic albuminuria; Moxson's albuminuria of adolescence (intermittent or remittent).
    - (*b*) Renal: In the course of nephritis urine may be free from albumin, especially in cases of chronic interstitial nephritis. At some hours of the day urine contains no albumin, at others it does.
    - (*c*) Accidental: Due to affections of the ureters, urethra, prostate, etc. Morning urine usually contains albumin.

It will be seen from this table that the mere fact that the urine contains albumin does not mean that the patient has nephritis, although this was the general view formerly, and many of the older practitioners still cling to it to-day. No diagnosis of Bright's disease can be made from the presence of albumin alone. Another point to be remembered is that the quantity of albumin present is not a measure of the extent or advancement of a renal lesion. Indeed, in the worst cases of chronic Bright's disease—interstitial nephritis—albumin is frequently present in very small quantities and often temporarily or permanently absent. In the presence of an acute inflammatory process in the kidney or of a chronic parenchymatous nephritis the variations in the daily amount of albumin, taken together with the amount of urea, the number of casts, etc., may assist in determining the prognosis of a case.

The physician must be on his guard against the false alarms of accidental albuminurias and the comparatively less important types of albuminuria grouped under the heading of circulatory, febrile, hematogenous, and intermittent. A careful study of all the clinical features in the case, especially as to the periodicity of the symptom, the quality of the proteid substance found, the condition of the circulation, and the presence of microscopic features indicating renal disease is the basis of accurate diagnosis in such cases.

METHODS OF TESTING FOR ALBUMIN.

Heat Test.—With Nitric Acid.—A test-tube is filled with clear urine,* and the upper portion of the fluid is heated to boiling. If the heated portion becomes cloudy, even in the slightest degree, as we can see by holding the tube against a black surface, the turbidity is due either to albumin or to earthy phosphates. If the cloudiness is due to the latter, it disappears on adding a few drops of nitric acid; if it is due to albumin, it remains. If no precipitate appears, or if the precipitate redissolves on shaking upon the addition of the acid, two or three more drops of the acid are added, and if a flocculent precipitate results, albumin is present.

Under favorable conditions heat will detect one part of albumin in 100,000 parts of urine, but there are many sources of error in the test by heat. The effects of the presence of earthy phosphates have already been spoken of. Another source of error is the fact that if there is very little albumin, the amount of acid will be in excess and the albumin will dissolve; on the other hand, if both phosphates and albumin are present and too little acid be used, the acid is taken up by part of the phosphates, while the remainder of these salts unite with the albumin to form soluble alkaline albuminates, the urine remaining clear.

Very highly acid urine from natural causes may fail to precipitate albumin by heat on the addition of acid, owing to the fact that a soluble acid albumin is formed under these conditions. The latter may be precipitated on the further addition of nitric acid or on neutralizing with potassium hydrate. There is a danger, however, of converting the albumin into soluble alkali albumin with the least excess of alkali, and so redissolving the precipitate. Highly alkaline urine converts the albumin into a soluble alkali albumin which is non-coagulable by heat, like the acid albumin. In this case the addition of a few drops of dilute acid will convert the alkali albumin into serum-albumin, which will be precipitated by heat.

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* When the urine is not clear, it should be filtered before apply-g any of these tests.

If the test-tube is not clean and happens to contain a drop of nitric acid, boiling may fail to cause a cloud on account of the conversion of serum-albumin into non-coagulable acid albumin. A flocculent precipitate formed *before* the addition of acid in the heat test may be calcium phosphate, which is soluble in an excess of acid. Such a precipitate occurring *after* the addition of acid is albumin. The urine should not be heated after the addition of the acid, as the coagulated albumin is soluble in the heated acid, and this is the reason why this test is not good for very small amounts of albumin, as the latter may be dissolved upon the addition of the acid if the fluid is hot enough.

Another source of error is the presence of uric acid or urates, which may give rise to precipitates that are crystalline (not flocculent) and which do not appear if the urine be diluted with three parts of water before the test. The precipitate of uric acid is dark brown in color, and does not fall until the specimen begins to cool. The presence of resinous acids in cases in which copaiba, cubebs, turpentine, benzoin, sandalwood oil, or Peru or tolu balsams has been taken gives a precipitate which dissolves in alcohol, while albumin is precipitated by this substance. Urines full of bile-pigments at times give a precipitate of biliverdin, but this is soluble in alcohol.

With Acetic Acid.—The heat test may be performed in the same manner with acetic acid, and the same sources of error obtain in this test as in the heat-and-nitric-acid test. The reaction is obtained as follows: The urine, if it has been found alkaline, is rendered slightly acid with a few drops of 2 per cent. acetic acid. The upper portion of the test-tube is boiled. The flocculent precipitate which results may be either albumin or it may be partly composed of nucleo-albumin and partly of serum-albumin. If one-fifth volume of a saturated sodium-chlorid solution be added, then a few more drops of the acid, and the mixture be boiled again, nucleo-albumin and mucin, if present, are not precipitated, while the serum-albumin is thrown down. If the urine is allowed to cool and if the coagulated albumin is removed by filtering, there may be a precipitate appearing on standing, which consists of albumoses, but this appears only if the urine contains a considerable quantity of sodium chlorid.

Purdy* gives the following method of performing this test, and commends it highly for distinguishing minute quantities of albumin. A test-tube is filled about two-thirds full of the previously filtered urine, and about one-sixth of this volume of a saturated sodium-chlorid solution is added. Next, from five to ten drops of acetic acid (50 per cent.) are added, and the upper portion of the contents of the test-tube is boiled for half a minute, giving a precipitate if albumin be present.

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* "Practical Urinalysis," Philadelphia, 1900, fifth ed., p. 72.

The Nitric-acid Test (*Heller's Test*).—This test is exceedingly sensitive, and for all practical purposes is probably the best. The urine should be filtered, even though it appears perfectly clear. A small amount of pure, colorless nitric acid—HNO_3 (c. p.)—is poured into a small test-tube; the latter is held obliquely in the left hand, while the urine is allowed to trickle down the side of the tube from a pipet consisting of a glass tube six or eight inches long, and drawn to a point. The urine will overlie the acid if it has been poured in gently enough. If albumin is present, a distinct, sharp, white zone will appear at the junction of the two fluids, varying in thickness—not according to the amount of albumin, but according to the rapidity with which the urine is poured and also according to the effervescence that follows the addition of the urine (Ogden). The band may vary from one-thirty-second to one-half inch in width, and in the presence of large quantities it is narrow, but very dense. If minute traces are present, it takes the shape of a hazy ring or cloud, which becomes more distinct after a few minutes.

Another way of performing this test is to pour the urine into the tube first and to allow the acid to pass down the side and under the urine. This manner of using nitric acid is not so convenient as the first.

Still another method involves the use of a small wineglass. This is filled one-half full of the filtered urine, the glass is inclined so that the urine reaches nearly to its edge, and the nitric acid is poured under the urine, as slowly as possible, from a small bottle, until the acid reaches about one-third the volume of the urine. The objections to this method are that it requires more acid and is not so convenient as the test-tube method. Ogden prefers this method above all others, and suggests that if in every case the proportion of urine and acid is kept the same and the nitric acid is poured from the bottle as slowly as possible, the appearance of the zone obtained may be used to determine approximately the amount of albumin in the urine. The slightest possible trace can be seen with this method only if the wineglass is perfectly clean and is held against

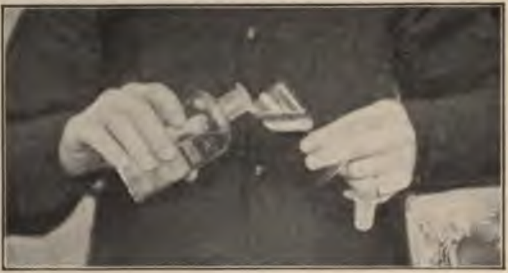

Fig. 6.—Method of performing the nitric-acid test for albumin (Ogden).

a black background, adjusted obliquely, as shown in the figure (Fig. 7). A "very slight trace" is shown by a zone, which can be seen by using a dark background, but cannot be seen if the observer looks down on the surface of the urine in the wineglass. A "slight trace" is a distinct zone of white which can be seen without a dark background and appears as a faint cloud when looking from above. A "trace" is a zone more distinct than those mentioned, and the cloud seems, on looking through the urine, so dense as to hide the bottom of the wineglass. Larger amounts give more prominent zones, which increase in flocculence and in density with the quantity of albumin present.

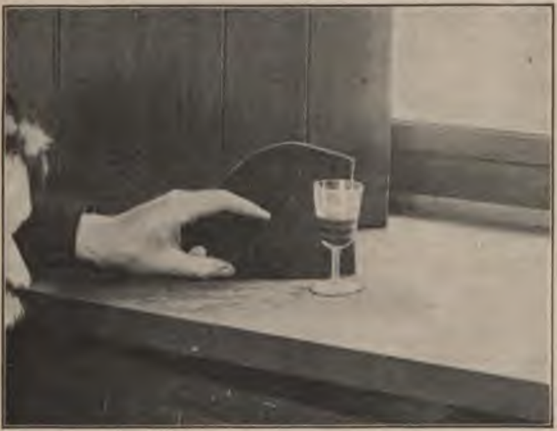

Fig. 7.—Method for the detection of minute quantities of albumin. Lower zone, albumin; upper zone, acid urates (Ogden).

Precautions in Using Heller's Test.—When nitric acid is placed in contact with normal urine, a brown ring appears which increases on standing and is due to the action of the acid on the coloring-matters. In urine with much coloring-matter the albumin, if present, will also be colored brown, or if there is much indican, the albumin ring will assume a reddish or violet tinge; if much blood-coloring matter, a brownish-red; if biliary pigments, a green color.

The overlying of nitric acid with urine precipitates the albumin as acid albumin, since the latter is not soluble in the excess of acid at the point of contact. Mucin is also precipitated, but is dissolved by the excess of nitric acid at the point of contact, and therefore does not form part of the ring. Peptones are not precipitated in this test, but albumoses and resins are. The differentiation from resins is best made by using some other test which does not precipitate the latter (sulpho-salicylic acid). Nucleo-albumin gives a ring which is fainter and is about one centimeter above that due to albumin. A white zone is also formed by the action of nitric acid on the mixed urates if these are in excess. This zone of acid urates is found over the zone of contact between the acid and the urine; it tends to diffuse rapidly into the urine above, and is dissipated on the cautious application of heat. If uric acid is present in large amounts, urea nitrate precipitates in crystals, but this can occur only in very concentrated urines.

If there is a large amount of carbonic acid and ammonium carbonate, as after alkaline fermentation, a vegetable diet, etc., the contact of urine with nitric acid produces so much effervescence that the test cannot be used. In this condition the following method (Hoffmann and Ultzmann) may be used: Add to the urine about a fourth part of potassium hydrate solution, warm the mixture, and filter; if the fluid is still cloudy and cannot be cleared by ordinary filtration, add one or two drops of the magnesium solution (see p. 201), warm again, and filter. The urine thus cleared will show albumin with Heller's test.

In the presence of resins, coloring-matters, etc., rings of precipitate which are soluble in alcohol will occur (compare under Heat Test with Nitric Acid, p. 56).

Other Tests for Albumin.—The heat test and Heller's test are the most important modes of detecting albumin. They are usually sufficient, but in case of doubt, and when we desire extreme delicacy, the tests which follow may be used. In practice it is a much better plan to use one or two tests as a matter of routine, to know these tests with all their possibilities and fallacies, and not to burden one's self with too many tests and reagents. Many of these less important tests are very sensitive, but clinically extreme delicacy is not desirable, as it leads to confusion when we remember that normal urine contains traces of albumin.

Picric-acid Test (*Johnson's*).—Into a test-tube six inches long pour four inches of filtered urine. Hold the test-tube obliquely and gently pour an inch of a saturated solution of picric acid over the surface of the urine. To make the reagent add six or seven grains of picric acid to one ounce of boiling distilled water. In the portion of the tube where the reagent mixes with the urine a yellow turbidity of coagulated albumin will appear. If the amount of albumin is small, the upper part of the tube may be heated to increase the turbidity. Picric acid precipitates, besides albumin, urates, peptone, albumose, the vegetable alkaloids, and mucin, all of which, except mucin, are dissolved with moderate heat. There must be an actual mixture of the urine with the reagent, not a mere surface contact.

Sodium-tungstate Test (*Oliver's*).—The reagent consists of equal parts of a saturated solution of sodium tungstate (1:4) and a saturated solution of citric acid (10:6). The specific gravity of this fluid is 1214, and it is best used by the overlaying method. It is a very sensitive test, but has the disadvantage of precipitating, in addition to albumin, acid urates, peptones, and mucin, although, unlike picric acid, it does not give any reaction with the alkaloids. The precipitates other than albumin are promptly dissipated by heat.

Potassio-mercuric-iodid Test (*Tanret's*).—This is very sensitive and is prepared as follows: Mercuric chlorid, 1.35 gm.; potassium iodid, 3.32 gm.; acetic acid, 20 c.c.; distilled water, enough to make 100 c.c. The two salts should be separately dissolved in portions of the water and the solutions mixed. The reagent is heavy, and is used by the contact method without previously acidulating the urine. It precipitates the same substances as picric acid, and the precipitates are also dissipated by heat or alcohol; they reappear on cooling. According to Oliver, the precipitate of nucleo-albumin is not dissolved by heat if a large excess of the reagent is used. Albumin gives a white, sharply defined zone.

Trichloracetic-acid Test (*Raabe, Grosstern, and Fudakovsky's*).—A saturated solution of the crystals of trichloracetic acid (one-half ounce of the crystal to two drams of water) is made and used by the contact method. It is claimed by some not to precipitate peptone or nucleo-albumin, and is esteemed very highly as a delicate test. The trouble with it is that it is too delicate, as it precipitates mucin and therefore cannot be regarded as trustworthy. It also precipitates albumoses, alkaloids, and sometimes uric acid, all these disappearing on the addition of heat.

Formalin Test (*Iatrona's*).—One c.c. of formalin solution (40 per cent.) is added to 5 or 6 c.c. of urine, which must be clear. Turbidity and a flocculent precipitate mean the presence of albumin. The test is hastened by heating the mixture.

Mercuric-chlorid-Formalin Test (*Pollacci's*).—A modification of Spiegler's well-known reagent was suggested by Pollacci. The solution consists of tartaric acid, 1 gm.; corrosive sublimate, 5 gm.; sodium chlorid, 10 gm.; formaldehyd (40 per cent.), 5 gm.; and distilled water, 100 c.c. It is applied by the contact method, and gives a white ring with albumin. The precipitate formed by adding the reagent to urine, if soluble on shaking, is due to phosphates or carbonates; if soluble by heat, it is due to peptones or alkaloids; and if insoluble by heat, it is due to albumin or globulin. It is said that Pollacci's test detects one part of albumin in 370,000 parts of urine.

Potassium-ferrocyanid Test.—To 10 c.c. of urine add 5 drops of strong acetic acid. If a precipitate appears, it is due to nucleo-albumin and should be filtered off. Then a few drops of a 5 per cent. solution of potassium ferrocyanid are added, and the turbidity, varying from slight opalescence to a denser cloud, shows the presence of albumin. An excess of the reagent will dissolve the precipitate, which is best observed by holding the test-tube in front of a black surface and by comparing it with a test-tube of normal urine. Albumose and nucleo-albumin give precipitates, the former dissolving with heat, the latter, on the addition of a few drops of lead-acetate solution. An excess of this solution will also dissolve the albumin.

Potassium Sulphocyanid Test (*Zouchlos'*).—A few drops of a mixture of 100 c.c. of potassium solution (10 per cent.) and 20 c.c. of acetic acid are added to urine. A cloud or precipitate occurs if albumin is present, and the test is said to detect 0.007 per cent. of the proteid (Schick).

Mercuric-chlorid Test (*Spiegler's*).—The reagent consists of 8 gm. of mercuric chlorid, 4 gm. of tartaric acid, and 20 gm. of sugar in 200 c.c. of distilled water. It is used by the contact method, like Heller's test. In the presence of albumin a sharply defined white ring appears. This test reacts with globulin and albumoses, but not with peptone.

Metaphosphoric-acid Test (*Grigg's and Hindenlang's*).—A little of the solid acid is mixed with the filtered urine and shaken. A turbidity results if albumin is present. This test reacts with albumoses and with uric acid, but these precipitates are dissipated by heat.

Salicylsulphonic-acid Test (*Sulphosalicylic-acid Test; Roch and Macwilliams'*).—Add one or two drops of a saturated solution of the reagent, or more if the urine is alkaline, to about twenty drops of the urine in a small test-tube. On shaking, opalescence or turbidity immediately appearing, shows albumin. Turbidity occurring slowly implies minute traces. On boiling, the precipitate is due to albumin or globulin.

Phenic-acetic-acid Test (*Méhu's and Millard's*).—The formula for this is: Glacial phenic acid, 2 dm.; acetic acid (c. p.), 6 dm.; potassium-hydrate solution, from 6 dm. to 2 oz. Apply by the usual contact method. It reacts with peptone, nucleo-albumin, albumoses, and alkaloids, all of which precipitates are said to disappear with heat. It is supposed to detect one part of albumin in 200,000 parts of urine.

Nitric-magnesium Test (*Roberts'*).—The solution is composed of one part of strong nitric acid and five parts of saturated solution of magnesium sulphate, making a mixture safe to handle. It is applied by the usual contact method. It is more sensitive than Heller's test. In the author's e rience with this reagent, which has been extensive, its delicacy has been found rather confusing clinically. It shows a double or triple ring, the lowest and densest of which is due to albumin, the upper to nucleo-albumin or urates, or both. Urine which does not show a ring with Heller's test occasionally shows a faint reaction, especially on standing, with Roberts' test. Unless the lower ring is sharply defined, dense, and appears almost instantly, clinical albuminuria cannot safely be diagnosticated with Roberts' test. It is most conveniently employed in the simple glass instrument known as the horismascope, or albumoscope. (See Fig. 8.) The urine is poured into the large end of the tube, and Roberts' solution is then poured down the small funnel, until the level of the solution reaches about the center of the black background in the larger tube. The rings are seen very distinctly against this background. The instrument can also be used with Heller's and with many other tests.

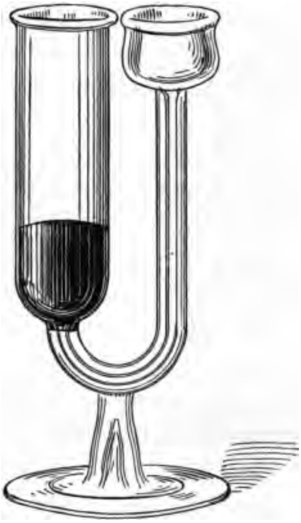

Fig. 8.—The horismascope.

Acidulated-brine Test (*Roberts'*).—A pint of saturated solution of common salt is mixed with an ounce of hydrochloric acid and the mixture filtered. It is used by the contact method, but is unsatisfactory, and its only advantage over nitric acid is that it is less caustic.

Mercuric-chlorid-and-citric-acid Test (*Stütz and Fürbringer's*).—A mixture of the double salt of mercuric chlorid and sodium chlorid with citric acid is put up in gelatin capsules. A solution of this reagent is not so sensitive as Tanret's, does not precipitate alkaloids, but sometimes gives opacity in urines that do not contain albumin. Concentrated urines which contain much uric acid must be diluted before using this reagent.

Sodium-nitroprussiate Test (*Mya's*).—This is a substitute for potassium ferrocyanid. The urine is first acidulated with acetic acid, and a concentrated solution of the reagent is added. The reagent must be kept away from light.

Resorcin Test (*Carrez's*).—One gm. of resorcin is dissolved in 2 c.c. of distilled water in a test-tube, and the urine is poured upon the surface. A white ring shows albumin. Peptone also gives a white ring, but it disappears on immersing the tube in boiling water.

Other Tests.—A great variety of substances besides those named has been employed to precipitate albumin. It would be useless to enter into a description of all these tests. Examples are: Asaprol and aseptol (Riegler's); tannin (Almén's); sodium sulphoantimoniate (Schlippe's); potassium antimoniate (Palm's); phosphomolybdic acid (Sonnenschein's); chromic acid (Kirk's); iodin and potassium iodid (Cohen's); calcium chlorid and hydrochloric acid (Jolles').

Comparative Delicacy of Various Tests.—It is very difficult to decide as to the comparative delicacy of a given test, and statements of different authors markedly conflict on this subject. There are many sources of error, especially when the amount of albumin is very minute, as we have seen in the consideration of the various tests. Approximately, however, Spiegler's is the most delicate test; next come trichloracetic and sulphosalicylic acids; then the heat test with acid; the ferrocyanid test; Roberts' test; Heller's test, and boiling with neutral salts and acids. In practice it is rarely necessary to use any tests beyond the heat test, Heller's, and occasionally Roberts' or Spiegler's. Every worker has his favorite tests, but it is important that he should know the limitations of the tests he uses and should avoid errors by carefully controlling his work with some standard test, like Heller's, which, after all, is the most satisfactory test clinically.*

QUANTITATIVE TESTS FOR ALBUMIN.

Gravimetric Method.—This is the only accurate method of determining the amount of albumin, but is entirely too elaborate for clinical work. It consists of boiling a certain volume of urine, to which enough acid has been added to render it distinctly acid in reaction. The coagulum is collected upon a dry, weighed filter; washed, dried, and weighed again. The increase in weight in the filter corresponds to the amount of albumin by weight in the given volume of urine.

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* Some of the reagents can be obtained in the form of papers, 'apsules or tablets for bedside testing; but at best these are makehifts.

Another method is to remove the albumin by coagulation, to determine the diminution in specific gravity in the supernatant fluid, and to multiply this difference in specific gravity by 400 (Zahor's coefficient).

A third method is to determine the total nitrogen in a urine containing albumin (by Kjeldahl's method), and to find the difference in nitrogen in the same volume of the urine, deprived of albumin by coagulation, multiplying the difference by 6.3 (Van Nuyes and Lyons). A fourth method is to determine the difference in refraction between the urine containing albumin and the same urine after coagulation. The error is said to be very small (Ehlenger).

A variety of optic methods have also been used, but they are of no value clinically.

APPROXIMATE CLINICAL ESTIMATION.

The simplest and least accurate mode of estimating the percentage of albumin consists in boiling the urine with acid, allowing the coagulum to settle, and then measuring the comparative bulk of the precipitate as compared with the total volume of urine. It is this method that gave rise to the confusing expressions of 25, 50, 75, or even 100 per cent. of albumin, and its use has been encouraged by the introduction of graduated tubes devised for the purpose of indicating the relative bulk of the coagulum. Such quantities as 75 per cent. are obviously impossible when we remember that urine cannot possibly contain more than 5 per cent. of albumin by weight, the usual amounts measured being less than 1 per cent. This method of estimating the bulk of the coagulum is, therefore, very misleading.

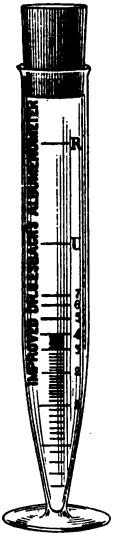


Fig. 9.—Esbach's albuminometer.

Esbach's Method.—This is the most convenient method of quantitative estimation of albumin, and if carefully performed, is sufficiently accurate for clinical purposes. A graduated glass tube, or albuminometer (Fig. 9), with walls rather thicker than the ordinary test-tube and provided with a rubber stopper, is the apparatus used. This tube is filled with urine to the letter U. Then Esbach's reagent is added up to the mark R. This reagent consists of 10 parts of picric acid and 20 parts of citric acid in 1000 parts of distilled water. The tube is closed with the stopper, and the urine and reagent are mixed by inverting the tube several times. It is then allowed to stand for twenty-four hours in a vertical position. The number at the level of the precipitate shows the number of grams of albumin contained in one liter of urine—that is, the number of parts per thousand. Each part per thousand represents $\frac{1}{10}$ of 1 per cent. by weight, so that 5 gm. per liter means 0.5 per cent. of albumin. It is best to use the latest form of Esbach's tube (Fig. 9), which has a foot and graduations in small fractions of one gram at the lower part, so that minute quantities of albumin can be estimated. For urines with large quantities of albumin—exceeding 0.7 per cent., which is the highest mark on the tube—we must use dilutions with equal parts of distilled water. The same procedure may be used when very small quantities of urine are available, the reading being, of course, multiplied by the number of times the urine has been diluted.

Centrifugal Method (*Purdy's*).—For this purpose a centrifuge revolving at a uniform speed of 1500 revolutions a minute and a special percentage tube, holding 16 c.c., are employed. To 10 c.c. of the urine add 3 c.c. of a 10 per cent. solution of potassium ferrocyanid and 2 c.c. of 50 per cent. acetic acid. Allow to stand for ten minutes, to insure the entire precipitation of the albumin. Place the percentage tube in a centrifuge with a radius, with tubes extended, of exactly $6\frac{3}{4}$ inches; revolve at 1500 revolutions a minute for three minutes, and read off the bulk percentage. This method is simple, accurate, and convenient, provided it be performed exactly as prescribed. According to Purdy, each $\frac{1}{10}$ c.c. of precipitate represents one per cent. bulk measure of albumin. Ogden found that in order to find the percentage of albumin by weight from this bulk measure we must divide the latter, expressed in $\frac{1}{10}$ c.c., by 6. The great source of error in this method is an excess of urates, which adds to the bulk of the precipitate. When this is known, it is better to centrifuge the precipitate, decant the supernatant fluid; to add hot water, which dissolves the urates, and to centrifuge again. The most important part of this method is to allow the precipitate to settle thoroughly before centrifuging.

The table on p. 73 from Purdy will serve to convert bulk-percentage into weight-percentage.

Vassilieff's Method of Titration.—This consists in titrating the urine with a solution of sulphosalicylic acid until all the albumin is precipitated, and then obtaining an end-reaction for the excess. The urine, which is rendered slightly acid with acetic acid, is measured off in a 10 c.c. pipet and diluted with water to 50 c.c. Two drops of a watery one per cent. solution of a yellow dye, known as "Echtgelb," are added, and the whole is titrated with a 25 per cent. solution of sulphosalicylic acid until the mixture takes on a permanent brick-red color. The amount of albumin can be computed by multiplying the number of cubic centimeters of sulphosalicylic acid used by 0.01006 (F. C. Wood).

PURDY'S QUANTITATIVE METHOD FOR ALBUMIN IN URINE (CENTRIFUGAL).

Table showing the relation between the volumetric and gravimetric percentage of albumin obtained by means of the centrifuge with radius of six and three-quarter inches; rate of speed, 1500 revolutions per minute; time, three minutes.

Volumetric Percentage by Centrifuge.	Percentage by Weight of Dry Albumin.	Grains per Fluidounce Dry Albumin.	Volumetric Percentage by Centrifuge.	Percentage by Weight of Dry Albumin.	Grains per Fluidounce Dry Albumin.	Volumetric Percentage by Centrifuge.	Percentage by Weight of Dry Albumin.	Grains per Fluidounce Dry Albumin.
¼	0.005	0.025	13½	0.281	1.35	31½	0.656	3.15
½	0.01	0.05	14	0.292	1.4	32	0.667	3.2
¾	0.016	0.075	14½	0.302	1.45	32½	0.677	3.25
1	0.021	0.1	15	0.313	1.5	33	0.687	3.3
1¼	0.026	0.125	15½	0.323	1.55	33½	0.698	3.35
1½	0.031	0 15	16	0.333	1.6	34	0.708	3.4
1¾	0.036	0.175	16½	0.344	1.65	34½	0.719	3.45
2	0.042	0.2	17	0.354	1.7	35	0.729	3.5
2¼	0.047	0.225	17½	0.365	1.75	35½	0.74	3.55
2½	0.052	0.25	18	0.375	1.8	36	0.75	3.6
2¾	0.057	0.275	18½	0.385	1.85	36½	0.76	3.65
3	0.063	0.3	19	0.396	1.9	37	0.771	3.7
3¼	0.068	0.325	19½	0.406	1.95	37½	0.781	3.75
3½	0.073	0.35	20	0.417	2.	38	0.792	3.8
3¾	0.078	0.375	20½	0.427	2.05	38½	0.801	3.85
4	0.083	0.4	21	0.438	2.1	39	0.813	3.9
4¼	0.089	0.425	21½	0.448	2.15	39½	0.823	3.95
4½	0.094	0.45	22	0.458	2.2	40	0.833	4.
4¾	0.099	0.475	22½	0.469	2.25	40½	0.844	4.05
5	0.104	0.5	23	0.479	2.3	41	0.854	4.1
5½	0.111	0.55	23½	0.49	2.35	41½	0.865	4.15
6	0.125	0.6	24	0.5	2.4	42	0.875	4.2
6½	0.135	0.65	24½	0.51	2.45	42½	0.885	4.25
7	0.146	0.7	25	0.521	2.5	43	0.896	4.3
7½	0.156	0.75	25½	0.531	2.55	43½	0.906	4.35
8	0.167	0.8	26	0.542	2.6	44	0.917	4.4
8½	0.177	0.85	26½	0.552	2.65	44½	0.927	4.45
9	0.187	0.9	27	0.563	2.7	45	0.938	4.5
9½	0.198	0.95	27½	0 573	2.75	45½	0.948	4.55
10	0.208	1.	28	0.583	2.8	46	0.958	4.6
10½	0.219	1.05	28½	0.594	2.85	46½	0.969	4.65
11	0.229	1.1	29	0.604	2.9	47	0.979	4.7
11½	0.24	1.15	29½	0.615	2.95	47½	0.99	4.75
12	0.25	1.2	30	0.625	3.	48	1.	4.8
12½	0.26	1.25	30½	0.635	3.05	. . .	. . .	. . .
13	0.271	1.3	31	0.646	3.1	. . .	. . .	. . .

Test.—Three cubic centimeters of 10 per cent. solution of ferrocyanid of potassium and 2 cubic centimeters of 50 per cent. acetic acid are added to 10 cubic centimeters of the urine in the percentage tube and *stood aside for ten minutes*, then placed in the centrifuge and revolved at rate of speed and time as stated at head of the table. If albumin is excessive, dilute the urine with water until volume of albumin falls below 10 per cent. Multiply result by the number of dilutions employed before using the table.

CHAPTER V.

OTHER PROTEIDS IN URINE.

GLOBULIN.

The tests that have thus far been described for albumin make no distinction between serum-albumin and serum-globulin; for, when we speak clinically of albumin in the urine, we mean the precipitate of albumin and globulin which results on testing for proteids in the urine. As these two substances almost always appear together, a differentiation of globulin from albumin and a knowledge of their comparative amounts do not seem of great clinical value. There are some cases, however, in which the presence of globulin has a special significance. It is noted in unusual quantities in the urine of catarrhal cystitis, in acute nephritis, and particularly in amyloid degeneration of the kidney and other conditions accompanied by considerable destruction of the renal epithelium. In chronic Bright's disease globulin is present in comparatively small amounts or is even absent. The distinction between serum-globulin and serum-albumin chemically is, therefore, a refinement of uranalysis which may sometimes be of value to the clinician.

Qualitative Tests.—1. A layer of faintly alkaline urine is floated over a saturated solution of $MgSO_4$, and the precipitate which results is globulin without the serum-albumin.

2. The urine is exactly neutralized, filtered, and saturated completely with magnesium sulphate at ordinary temperature, or with a saturated solution of ammonium sulphate. A white precipitate immediately forming is globulin. A precipitate appearing later with the use of ammonium sulphate may be ammonium urate.

3. If the globulin precipitate be filtered off, the same urine may be tested for serum-albumin by heating with a few drops of acetic acid.

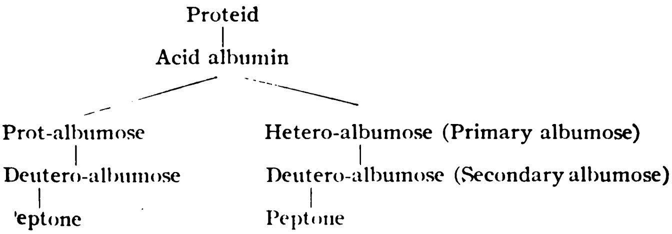
4. A very simple method is that of Roberts: A wineglass is filled with water, and a few drops of albuminous urine are allowed to fall into it. If globulin is present in any quantity, each drop is followed by a milky streak until the water assumes an opalescence which disappears on adding acetic acid.

Quantitative Test.—The amount of globulin may be determined separately from the albumin by carefully neutralizing the urine and by precipitating the globulin with an equal volume of saturated neutral solution of ammonium sulphate. The precipitate is thoroughly washed with saturated magnesium-sulphate solution, dried at 100° C., boiled with water, extracted with alcohol and ether, then dried, weighed, incinerated, and finally weighed again, the last weight being the amount of globulin.

ALBUMOSE.

A number of substances are formed in the digestion of the proteids by the gastric juice which differ in their properties from the original proteids ingested. The intermediate products between the original proteids and the final products of digestion (peptones) are called *proteoses*. These are subdivided into albumoses, globuloses, vitelloses, caseoses, etc., according to the proteids from which they are formed. Albumoses and globuloses do not appear in normal urine, but are present in some diseases. The characteristics of the proteoses are chiefly that they are uncoagulable by heat; are precipitated, but not coagulated, by alcohol, and are precipitated by nitric acid, the precipitate thus formed being dispelled by heat, but reappearing on cooling. They all respond to the biuret reaction. (See Detection of Peptone, p. 79.)

A simplified scheme of the products of digestion from the original proteïds is given below (Wood), the actual process being more complex. Of the substances appearing in this scheme, those which concern us are the primary and secondary albumoses and peptone.


Proteid
Acid albumin
Prot-albumose
Deutero-albumose
Peptone
Hetero-albumose (Primary albumose)
Deutero-albumose (Secondary albumose)
Peptone

Primary albumosuria is a very rare condition, the majority of the patients so far observed having had multiple sarcoma of the bone-marrow. The classic case of Bence-Jones has given his name to this form of albumosuria. The clinical significance of this albumosuria is very indefinite as yet, and no practical conclusions can be drawn from its presence.

Secondary albumoses are found in about 90 per cent. of the febrile diseases, in septic conditions like meningitis, empyema, etc. They are found in the urine in cases of intestinal ulcer of typhoid or dysenteric origin; less commonly, of tuberculous origin; in phosphorus-poisoning, in abscesses of the liver, and in malignant growths in any part of the body, probably as the result of ulceration.

Detection of Albumoses.—Albumoses are detected by their reactions and solubilities. *Primary albumose* (hetero-albumose) is insoluble in hot and cold water; is precipitated by dialysis from saline solution; is soluble in both hot and cold solutions of 10 per cent. sodium chlorid; is partly precipitated, but not coagulated, on heating to 65° C.; is precipitated by saturation with sodium chlorid or magnesium sulphate, or with saturated ammonium sulphate, or on the addition of nitric acid in the cold, the precipitate being dissolved with heat and reappearing on cooling.

Secondary albumose (deutero-albumose) is soluble in hot and cold water; soluble in hot and cold solutions of 10 per cent. sodium chlorid cipitated by saturation with sodium chlorid or magnesium sulphate, but is precipitated by saturation with ammonium sulphate. With nitric acid it is precipitated only in the presence of an excess of salts.

PEPTONE.

Peptone is the final product of proteid digestion. It is also the product of decomposition of albuminoids and blood-corpuscles. If peptones are hydrated still further, they are split up into simpler substances that are no longer proteids. Peptones are soluble in water; uncoagulable by heat; and are not precipitated by nitric acid nor by many of the precipitants of proteids. They are precipitated by tannin, picric acid, phosphotungstic acid, phosphomolybdic acid, and potassiomercuric iodid. Two forms of peptone are distinguished: (1) Hemipeptone, which, by the further influence of the pancreatic juice, is split up into leucin and tyrosin and other simpler products. (2) Antipeptone, which is not further decomposable by pancreatic juice; does not form tyrosin on the addition of sulphuric acid, nor respond to Millon's reagent. (See p. 88.) Peptones are readily diffusible by osmosis through animal membranes, while albumoses are only slightly diffusible, and albumin not at all so under ordinary conditions. Peptones differ from albumoses also by not being precipitated by saturation with ammonium sulphate.

Peptonuria.—Normal urine does not contain any peptone, but this substance has been found in the urine of phosphorus-poisoning, in suppurative conditions, lobar pneumonia, acute rheumatism, typhoid fever, typhus fever, small-pox, scarlet fever, mumps, tuberculosis, erysipelas, empyema, cancer, especially of the liver and intestine, etc. "Pyogenic peptonuria" is the result of the absorption into the circulation, and thence into the kidneys, of the products 50 of decomposition of the peptone-constituent of the leukocytes. This peptonuria is regarded as an evidence of suppurative changes in acute inflammatory conditions. A variety of applications in diagnosis based upon this principle have been suggested, and Maixner has laid down a law that whenever pus is forming in the organism, peptone is present in the urine. 30

Besides these pyogenic causes, the destruction of many blood-cells may be a source of peptone excretion, as in acute infectious diseases and in poisoning with blood-destructive poisons. Other causes are cancer of the liver, the latter organ in health possibly converting peptone into albumin; ulcers of the intestine, which enable peptones to pass directly into the blood from the intestine; peptonuria of puerperal women, which is said to be normal, and, finally, the appearance of peptone in the urine when the former is injected into the blood.

60

Detection of Peptone.—In order to detect peptone in the urine it is necessary to remove all traces of other proteids. For this purpose the urine must be treated in some way that precipitates the other albuminous bodies. 34

9, 20

Hofmeister's Method (*Precipitation with Phosphotungstic Acid*).—Fifty c.c. of urine are treated with acetic acid and boiling to remove the albumin and globulin. The filtrate is acidified with 5 c.c. of hydrochloric acid, and the albumoses, etc., are precipitated with from 2 to 3 c.c. of 10 per cent. phosphotungstic acid. The beaker should be heated very gently, so as to render the precipitate coherent. The precipitate is allowed to settle as a brownish-gray mass; the supernatant fluid is carefully decanted, and the mass washed twice with distilled water. The mass is next dissolved by heating, and the addition, drop by drop, of 30 per cent. ammonia solution. This gives a fluid which, if found to be of a bluish color, should be boiled with the addition of more alkali until it becomes colorless. This fluid contains peptone in solution and can be tested with the *biuret test* as follows:

To the cooled fluid in a narrow test-tube add one drop of a one per cent. solution of copper sulphate, the resulting amethyst-red color being characteristic. It should be noted that urine very rich in urobilin may give this test in the absence of peptone, if large quantities are used, and that in such cases only 10 c.c. should be employed.*

Another method with phosphotungstic acid, according to Hofmeister, consists in adding $\frac{1}{5}$ volume of concentrated acetic acid to the urine, and then some solution of phosphotungstic acid. If the urine remains clear after standing for a considerable while, no peptone is present; but if the urine shows cloudiness after ten minutes, peptone may be present, although the negative results of this test are not trustworthy.

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* This method with phosphotungstic acid is more delicate and satisfactory than the same author's method with tannin.

A simpler method is as follows: Saturate the urine, after slightly acidifying with acetic acid, with ammonium sulphate; filter any precipitate, which consists of albumin, globulin, or albumose. In the filtrate the peptone will remain and be precipitated with potassiomercuric iodid.

Ralfe's Test.—When large quantities of peptone are present, a sufficiently accurate test is performed by placing a dram (3½ c.c.) of Fehling's solution in a test-tube and overlaying it with an equal bulk of urine. A zone of phosphates forms at the point of contact, and a delicate rose-colored halo will float over this if peptones are present. If albumin is mixed with the peptones, the halo is purple.

DIFFERENTIATION OF ALBUMIN, GLOBULIN, ALBUMOSE, AND PEPTONE.

Albumin, globulin, albumose, and peptone, the four types of proteids considered thus far, may all be present in the urine at the same time, and although this is very rare, yet it is useful to be able to differentiate them by means of a single series of tests which will bring out the presence of each separate type. The best method for this purpose is that of Halliburton, which is as follows:

1. If the urine gives no precipitate on boiling after acidulation, albumin and globulin are abse

if a precipitate occurs, albumin or globulin, or both, are present.

2. If the urine after neutralization gives no precipitate on saturation with magnesium sulphate, globulin and primary albumose are absent; if such precipitate occurs, one or the other is present.

3. If the urine is saturated with ammonium sulphate and filtered and the filtrate gives no xanthoproteic* or biuret† reaction (a large excess of potash must always be added), peptone is absent.

4. If the urine gives no precipitate on boiling after precipitation; no precipitate with nitric acid, and no precipitate on adding ammonium sulphate to saturation, peptone can be the only proteid present. Confirm this by the biuret reaction (see p. 80).

5. If all proteids are present, they may be separated as follows:

Saturate the urine (faintly acidified with acetic acid) with ammonium sulphate: a precipitate is produced; filter.

(*a*) *Precipitate.*	(*b*) *Filtrate.*
Contains albumin, globulin, and primary and secondary albumoses.	Contains peptone.

Collect the precipitate on a filter, wash with saturated solution of ammonium sulphate, and redissolve it by adding a small quantity of water. To this solution add ten times its volume of alcohol: precipitate forms. Collect this, and let it stand bsolute alcohol for from seven to fourteen days.

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e p. 88.

† See p. 80.

Then filter off the alcohol; dry the precipitate at 40° C., extract with water, and filter.

(*a*) *Residue.*	(*b*) *Extract.*
This consists of albumin and globulin coagulated by alcohol.	This contains the albumoses in solution.

Primary albumose is precipitated by heating the solution to 65° C. or by saturating a portion of the extract with magnesium sulphate. Secondary albumose remains in solution.

Take another portion of the urine, neutralize it, and saturate with magnesium sulphate: a precipitate is produced; filter.

(*a*) *Precipitate.*	(*b*) *Filtrate.*
This consists of globulin and primary albumose, which may be separated by the prolonged use of alcohol as above.	This contains albumin, secondary albumose, and peptone. Add alcohol as above; in seven days albumin is rendered insoluble in water. The secondary albumose and peptone are soluble and may then be separated by ammonium sulphate.

NUCLEO-ALBUMIN AND MUCIN.

The urine may contain a number of substances which form gelatinous, stringy masses like the mucus of the saliva. These are chiefly important because they are likely to be mistaken for albumin and are present in normal urine in very small amounts.

Mucin.—This is present in urine partly in solution and partly in a faint cloud already spoken of as the *nubecula.* The mucus which forms this cloud is derived from the secretion of the urinary tract. This mucin is precipitated in pure form by acet acid and is the same as the nucleo-albumin tioned below, but is easily distinguishable by the fact that it is soluble in a slight excess of the acid. It is not precipitated by boiling the acidulated solution. In the urine it is kept in solution after the addition of the acid by the salts present, so that it is not usually precipitated. It is also precipitated by inorganic acids, by Esbach's reagent, etc., but is easily dissolved in an excess of any of these, hence does not interfere with the ordinary tests for albumin. The only metal capable of precipitating mucin is lead. Mucin is distinguished chemically from the nucleo-albumins by the fact that its molecule contains no phosphorus, but instead contains a substance which reduces Fehling's solution (see Tests for Glucose, p. 91), especially if the mucin has been heated with dilute hydrochloric acid. Mucin is not of any clinical importance in uranalysis as regards renal disease.

Nucleo-albumin.—A nucleo-albumin is a combination of a nuclein with some albuminous matter. A nuclein is a combination of some form of proteid matter with nucleic acid (Chittenden). A certain amount of nucleic acid is present in normal urine, and is combined usually with the small traces of serum-albumin that exist normally in the excretion.*

Nucleo-albumin is, therefore, a combination of albumin with nucleic acid. It contains about 1.5

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* Besides, there are two other organic acids that exist in the urine in small amounts—chondroitin-sulphuric and taurocholic acids—proteids which also combine with traces of the taurocholic being abundant in the urine of jaundice.

per cent. of phosphorus, is amorphous and insoluble in water, but dissolves in weak solutions of neutral salts.

Clinical Significance.—Traces of nucleo-albumin occur in the normal urine. Larger amounts are to be found in the urine of the newly born; after overexertion; in inflammation of the urinary tract; in leukemia; in acute diseases, especially such as affect the kidney; after injuries to the kidney, and after chloroform narcosis. It is abundant in patients suffering from jaundice. There is no nucleo-albumin excreted from the blood in any of these conditions, but an increase of nucleo-albumin always indicates an irritation or inflammation of the urinary tract. In cystitis and other bladder diseases the thick, stringy substances passed by the patients contain a great deal of nucleo-albumin from the nuclei of the leukocytes and pus-cells which collect in the bladder. In women an increased amount of nucleo-albumin is often present, chiefly from the vaginal secretion; and it is important to remember this, as in specimens of urine from women one is more apt to mistake this substance for albumin.

Detection of Mucin and of Nucleo-albumin.—To detect mucin the urine should be diluted with water, otherwise uric acid may be precipitated by this reaction. After dilution, an excess of acetic acid should be added. The precipitate may be purified by dissolving in water with a little sodium hydrate, and again precipitating by acetic acid. To distinguish nucleo-albumin from mucin the precipitate must be boiled with a dilute mineral acid, and if no copper-reducing substance is found by this means, mucin is absent.

Ott's Method for Nucleo-albumin.—To the urine add an equal amount of saturated solution of sodium chlorid, and to this mixture add slowly Almén's tannin solution. The latter consists of 5 gm. of tannin; 10 c.c. of 25 per cent. acetic acid; 240 c.c. of 40 per cent. methyl-alcohol. An abundant precipitate will appear if nucleo-albumin is present.

Nucleo-albumin and mucin are apt to give rise to confusion in testing for albumin, especially with those tests which require previous treatment with acetic acid, which precipitates both mucin and nucleo-albumin. Purdy calls attention to the fact that by charging the urine with a concentrated sodium-chlorid solution before the addition of the acid both these bodies are subsequently held in solution in the presence of acetic acid and heat. With the ferrocyanid test also, if the reagent is added first to the urine, it acts like the salt solution and holds these bodies in solution, so that the subsequent addition of acetic acid does not affect them.

FIBRIN.

Fibrin is a product of coagulation of blood, lymph, transudates, or exudates. It is an elastic, white, stringy substance, insoluble in water, ether, and alcohol; soluble with difficulty in solutions of sodium chlorid (5 to 15 per cent.), of potassium nitrate (6 per cent.), and of magnesium sulphate (5 to 10 per cent.). When fibrin is dissolved in saline solutions, a globulin is found in the solution. Fibrin is coagulated by heat from its solutions, precipitated by saturating them in magnesium sulphate, and dialyzing the salts from these solutions. The addition of weak hydrochloric acid causes fibrin to swell up into a transparent jelly, while the addition of strong acids dissolves it with the formation of acid albumin or syntonin and albumoses. Pepsin and hydrochloric acid digest it, as does the pancreatic juice, the results being albumoses and peptone. Fibrinogen, which is the predecessor of fibrin in circulating blood, has been found to possess properties resembling those of globulin.

Clinical Significance.—Fibrin in the urine usually means the presence of blood, the quantity depending upon the extent of the hemorrhage. Sometimes fibrin is present when there are no blood-corpuscles, and the urine may coagulate spontaneously on standing, or throw down a sticky sediment.

Detection.—It is important to distinguish between fibrin and large amounts of pus forming a gelatinous, sticky mass. In the latter case, the addition of water thins the urine and the addition of an alkali forms a white precipitate of alkaline albuminate. To test a fibrin coagulum it should be separated by filtration and washed with water. The residue should show the chemic characteristics already detailed. A part of the mass may be treated with a dilute solution of sodium hydroxid. If it is insoluble on standing for a long while, it is probably fibrin, since albuminous bodies dissolve in this solution. A fibrin clot, however, dissolves completely if warmed gently for several hours on a water-bath with a 1 per cent. solution of sodium carbonate. This solution is filtered and treated with Millon's reagent, which gives a deep-red color.

GENERAL COLOR REACTIONS OF THE PROTEIDS.

Xanthoproteic Reaction.—Heat the solution of proteid with pure HNO_3. The yellow color changes to a deep orange on the addition of alkaline hydrates. When large amounts of proteids other than peptones or albumoses are present, a yellow precipitate occurs.

Millon's Reaction.—One part of metallic mercury is dissolved in 2 parts of nitric acid; evaporated to ½ volume, and 1½ parts of water are added. Allow to stand for twenty-four hours and decant. A drop of this reagent produces a precipitate which turns red on heating, or a red color on heating if the proteid is present in small amount.

Piotrowski's Reaction.—Add a concentrated sodium-hydrate solution to the urine containing proteids. Then add one or two drops of a dilute $CuSO_4$ solution, producing a violet color which deepens on boiling, or a rose-red (biuret reaction) color with peptone if care is taken not to add too much copper solution.

QUESTIONS ON CHAPTERS IV AND V.

Albumin.—What is usually meant by albuminuria? Can normal urine contain albumin? What proteid is present in normal urine constantly? What are the physical conditions for the excretion of albumin? What three factors determine albuminuria? What is meant by accidental albuminuria? What may it be due to? How is it distinguished? Name the causes of—(*a*) Nephritic albuminuria;

(*b*) circulatory albuminuria; (*c*) febrile albuminuria; (*d*) hematogenous albuminuria; (*e*) intermittent albuminuria. What is the value of albuminuria in the diagnosis of Bright's disease?

Describe the heat test with nitric acid. How is the cloudiness differentiated from that due to phosphates? What are the sources of error in this test? Describe the heat test with acetic acid. How do you distinguish nucleo-albumin in this test? What is Purdy's method of performing it?

Describe Heller's test. What are the different methods of performing it? What precaution should be taken in testing with this method? What is the value of the other tests for albumin in practical work?

What does picric acid precipitate besides albumin? Describe the tests with picric acid, sodium tungstate, formalin, potassium ferrocyanid, and nitric magnesium. What is the comparative delicacy of these tests?

What is the most accurate method of determining the ***amount of albumin*** in the urine? What other methods may be used for this purpose? What is the value of the method by "bulk percentage"? Describe Esbach's method; Purdy's centrifugal method; Vassilieff's method of titration.

What chemic substances do we mean by "albumin" in the urine? In what conditions is it useful to differentiate *globulin?* Describe Roberts' simple method of testing for globulin.

What are albumoses? In what conditions have primary *albumoses* been found in the urine? Secondary albumoses? What are the chief chemic features of these two classes of bodies? What is *peptone?* What are its chief chemic characters? What is the clinical significance of peptonuria?

Describe Hofmeister's method for peptone; Ralfe's test; the biuret test.

Why are *nucleo-albumin* and *mucin* important in urine analysis? Whence is mucin derived? What are its chemic properties? How does it differ from nucleo-albumin—(*a*) in its behavior to acetic acid? (*b*) in its molecule? What is a nucleo-albumin? A nuclein? What is the clinical significance of nucleo-albumin? What may it signify in women? How is mucin detected? Nucleo-albumin? What precautions should be taken in testing for albumin against confusion with these bodies?

Describe *fibrin* and its chemic characters. What does its presence in the urine indicate? How is it distinguished from pus precipitate?

Name three general *color reactions* of the proteids. Describe the xanthoproteic test; the biuret reaction.

II. CARBOHYDRATES.*

CHAPTER VI.

GLUCOSE.

($C_6H_{12}O_6$.)

The question as to whether glucose is present in normal urine has not been finally settled, although the latest researches of Wedenski apparently affirm this statement. For clinical purposes this question is not of importance, as the quantities of sugar that may be present in normal urine are so exceedingly small that they cannot be recognized by the ordinary tests such as are employed in routine examinations. Glucose is present in small quantities in normal blood, and this amount becomes greatly increased in some diseases, reaching its highest point—about 0.1 per cent.—in advanced diabetes.

Clinical Significance.—The presence of glucose in the urine is no more synonymous with diabetes than the presence of albumin is with Bright's disease, but diabetes is the condition which most commonly causes glycosuria. Diabetes is now assumed to be a disease of metabolism which prevents the conversion of the carbohydrates into their simpler elements. The anatomic site of the lesion is usually the pancreas; for most cases of diabetes show certain changes in this organ, especially in the islands of Langerhans.

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* A number of carbohydrates are met with in the urine, including glucose, levulose, lactose, etc. The general properties of carbohydrates should be known to the student, and should be studied in books on general chemistry. As in the case of proteids, there is one carbohydrate which is of great importance clinically, namely, glucose.

Besides diabetes, a series of other causes may produce glycosuria: Thus *alimentary glycosuria* is due to an excess of carbohydrates in the food; *medicinal glycosuria* is due to drugs, such as chloroform, amyl nitrite, phloridzin, the inhalation of illuminating gas, etc.; *secondary glycosuria* accompanies cirrhosis of the liver, severe injuries of the brain, apoplexy, paresis, and other nervous diseases; exophthalmic goiter, the removal of the thyroid, or the use of large doses of thyroid extract; a new growth in the pancreas or the occlusion of the pancreatic duct by a stone, followed by atrophy of the gland. Glycosuria may also occur during pregnancy, in the course of acute infectious diseases, such as diphtheria, and just before death in cases of chronic nephritis, possibly as the result of edema of the brain.

Detection of Sugar in the Urine.—The *copper tests* are the most commonly used for searching for glucose in the urine. They all depend upon the power of glucose to reduce copper oxid in an alkaline solution.

Trommer's Test.—This is the oldest of this group of tests. One-third of a test-tube full of urine is rendered alkaline with potassium hydrate, and to this mixture a weak solution (5 per cent.) of copper sulphate is added, drop by drop, shaking after each addition, until a deep-blue color is obtained, or until the copper hydrate, which forms as the solution is added, fails to dissolve. The upper portion of the mixture is next boiled, and if sugar is present, a yellow precipitate of copper suboxid will form. If the same method be pursued without heat and the test-tube allowed to stand for a day, a similar precipitate of cuprous oxid will appear. If the reaction is at all doubtful, it is better to follow the second method, without heat, since most of the other organic substances which reduce the salts of copper do so only when heated (Neubauer).

Precautions.—In all copper tests certain precautions should be taken: Albumin interferes with the reduction of the copper oxid and must always be removed. An excess of copper sulphate or too strong solutions should not be used, as prolonged boiling of any urine with a large excess of copper produces a yellow or greenish-yellow color which may appear when the mixture cools. Prolonged boiling should be avoided, half a minute being sufficient, as a reduction of copper by other organic substances than sugar follows prolonged boiling. There must be a yellow or red precipitate to make the reaction positive. A flocculent precipitate, transparent or pale grayish, is due to earthy phosphates. If these be precipitated before testing, by adding potassium hydrate, and filtered out, this error is eliminated. A change of color does not constitute a reaction. Copper oxid is sometimes reduced by other organic matters occurring in urine, the most important of which should be remembered;

they are: uric acid, creatinin, hippuric acid, urates, hypoxanthin, mucus, indican, and substances found after administering chloral, turpentine, etc. When the urine is very dark or scanty, an excess of uric acid may be suspected, and this source of error should be guarded against. It must be noted also that a small amount of sugar may be present and fail to reduce the copper in the presence of ammonium compounds, albumin, urinary coloring-matters, pepsin, peptones, and other organic matters. If the reduction is partial, the precipitate is yellowish green. When doubt exists as to the cause of the precipitate, the bismuth test or the fermentation test should be resorted to.

Fehling's Test.—The reagent consists of two parts, viz.: the copper solution and the alkaline solution.

COPPER SOLUTION.

Copper sulphate	34.639 gm.
Distilled water	1000 c.c.

ALKALINE SOLUTION.

Sodium-potassium tartrate (Rochelle salt)	173 gm.
Sodium-hydrate solution (sp. gr. 1120) *	500 c.c.
Distilled water, enough to make	1000 c.c.

These solutions must be kept in separate bottles in a dark place, and the stoppers should be greased with a mixture of vaselin and paraffin to prevent adhesion to the neck of the bottle. Twenty c.c. of the combined mixture (10 c.c. of each) require 50 mgm. of sugar to complete the reduction of the copper contained in this amount of solution.

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* The sodium-hydrate solution contains 52.727 gm. of caustic soda and enough distilled water to make 500 c.c.

Method of Testing with Fehling's Solution.—One c.c. of each of the solutions should be diluted with about four times the amount of water, and the mixture should be boiled for a few seconds. If the solution remains clear, the suspected urine should be added drop by drop. If sugar is present in considerable amount, the first two drops will cause a yellow precipitate, but the urine may be added slowly if no precipitate occurs, until an equal volume of urine has been added. The presence of sugar is characterized by a yellow or red precipitate of copper suboxid. If the precipitate does not appear until five minutes or longer after the addition of the urine, the quantity of sugar is less than one per cent. If no precipitate occurs within thirty minutes, allow the test-tube to stand for a day, as traces of sugar may show after a few hours. The urine may be gently heated, not boiled, before it is added to the solution, and *after the addition of the urine the mixture should not be boiled*, as this induces the reduction of copper by other substances than sugar and so leads to errors.

Fehling's solution, even if kept in two separate bottles, is not indefinitely stable, but decomposes very easily, and such an altered solution will give a precipitate on heating without the addition of glycosuric urine. Therefore the preliminary heating of the diluted urine is intended to show whether the reagent is fresh and trustworthy, in which case heating will not produce any decomposition and the reagent will remain clear. The value of Fehling's test as a routine method is universally acknowledged, and if performed properly, it is very trustworthy and exceedingly delicate.

Haines' test is a modification of Fehling's. It is claimed that the solution prepared according to Haines' formula is stable and keeps indefinitely, while the ordinary Fehling's solution does not. The improved formula consists of 30 gr. of copper sulphate, ½ oz. of distilled water, ½ oz. of pure glycerin, and 5 oz. of potassium-hydrate solution. The copper is dissolved in the water, the glycerin is mixed thoroughly, and the potash is added. A dram of this solution is gently boiled in a test-tube and six or eight drops (not more) of the suspected urine are added. The mixture is gently boiled, and if sugar is present, a copious yellow or yellowish-red precipitate appears.

Pavy's solution consists of:

Cupric sulphate	320 gr.
Neutral potassic tartrate	640 gr.
Caustic potash	1280 gr.
Distilled water	20 fl. oz.

This solution is made and used in the same way as Fehling's, but 100 min. correspond to ½ gr. of glucose, the formula for grape-sugar being here taken to be $C_6H_{14}O_7$ instead of $C_6H_{12}O_6$, as Fehling had it. It is used in the same way as Fehling's solution.

Phenylhydrazin Test.—The easiest way to perform this test is by Williamson's method, which is as follows: A test-tube of ordinary size is filled for about half an inch with phenylhydrazin hydrochlorate in powder; then sodium acetate, also in powder, is added for another half-inch. The test-tube is then half filled with urine and boiled over a spirit-lamp, the powders soon dissolving under the influence of heat. The urine is boiled for about two minutes, and the tube is then left to deposit a yellow sediment, which consists of needle-shaped crystals of a bright sulphur-yellow color—phenyl-glucosazone.

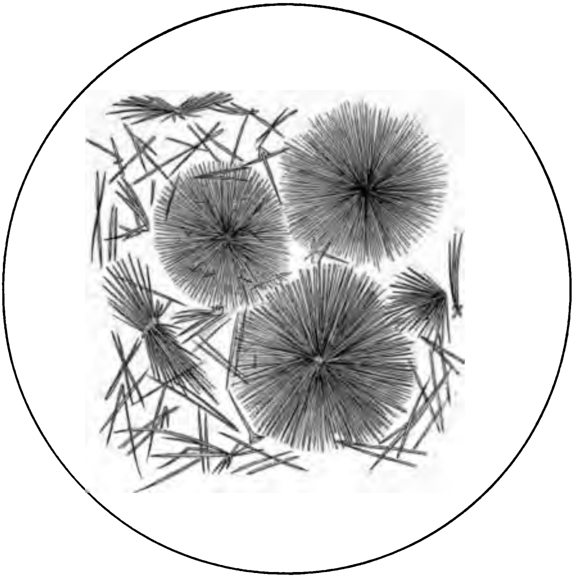
The great advantage of this test is that it gives no reaction with uric acid, creatinin, hippuric acid, etc., while with Fehling's test these substances are often a source of error. Phenylglucosazone ($C_{18}H_{22}N_4O_4$) crystallizes in fine yellow needles which are usually arranged in sun-burst fashion. They are almost insoluble in water, but dissolve in boiling alcohol and melt at 204° C. (See plate 2.)

Methylene-blue Test.—Methylene-blue is decolorized by glucose in a warm alkaline solution. To one part of the urine add nine parts of water. Two c.c. of this diluted urine are mixed with 6 c.c. of a 1:3000 solution of methylene-blue, and 2 c.c. of potassic hydrate are added. The mixture is boiled for one or two minutes, and if sugar is present, the blue color disappears. The fluid should not be shaken, as the blue color reappears, owing to the action of the oxygen in the air. This test is not so satisfactory as Fehling's nor the phenylhydrazin test.

Bismuth Tests.—These depend upon the power of glucose to reduce the salts of bismuth, giving a black precipitate of the metallic base.

Boettger's Test.—An equal volume of potassium-hydrate solution (U. S. P.) or of a solution of sodium

PLATE 2



CRYSTALS OF PHENYLGLUCOSAZONE (*after von Jaksch*).

carbonate (one part of crystals to three parts of distilled water) are mixed with the urine in a test tube; a small amount of bismuth subnitrate is added, and the mixture is shaken and boiled. If sugar is present, a black precipitate appears that adheres to the sides of the test-tube. If the amount of sugar is small, a gray precipitate appears. It is better to take a small amount of bismuth in making the test in such cases. The gray precipitate is said to occur sometimes when no sugar is present.

The difficulty with this test is that the urine must be free from albumin and other substances containing sulphur, as traces of sulphur form bismuth sulphid, which may be mistaken for metallic bismuth. To avoid this we may use:

Brücke's Modification of the Bismuth Test.—To remove the sulphur compounds Frohn's reagent is used. It consists of 1.5 gm. of freshly precipitated bismuth subnitrate mixed with 20 gm. of water and heated to boiling, whereupon 7 gm. of potassium iodid and 20 drops of concentrated hydrochloric acid are added. Ten c.c. of water are poured into a test-tube and the same bulk of the suspected urine is poured into another tube. To the water add a drop of Frohn's reagent, which will cause a precipitate. Then add, drop by drop, concentrated hydrochloric acid until the precipitate is redissolved. In this way we ascertain approximately the amount of reagent to be added to the suspected urine. Add the same quantity of hydrochloric acid to the urine in the other test-tube, then add the bismuth solution until precipitation is complete, and filter. Further addition of hydrochloric acid or of the reagent should not render the filtrate turbid. The filtrate is then boiled with an excess of alkali, as in Boettger's test. If sugar is present, a gray or black precipitate appears. According to Brücke, this test will detect 0.4 per cent. of glucose in water.

Nylander's Test.—Almén's reagent, which consists of 4 gm. of Rochelle salt in 100 c.c. of a 10 per cent. solution of sodium hydrate, is used. The solution is warmed, and 2 gm. of bismuth subnitrate are added. One part of this fluid is added to 10 parts of urine and the mixture heated. In from three to five minutes it turns black if sugar is present; the reaction is said to occur if over 0.1 per cent. of sugar is present, but it is not to be used in albuminous urines, and occurs in the presence of other reducing substances and of melanin.

Picric-acid-and-potash Test (*Braun's*).—This is based on the fact that grape-sugar, when boiled with picric acid and potash, will reduce the yellow picric to the deep-red picramic acid, the depth of color depending upon the amount of sugar present. To 1 fl.dm. of the suspected urine add 40 drops of a saturated solution of picric acid and ½ dm. of potassium-hydrate solution. Albumin, if present, will give a turbidity on the addition of picric acid, but this does not interfere with the test. The mixture is boiled, and if sugar is present, it turns a dark mahogany red. Normal urine also darkens somewhat under this treatment, but not so markedly.

Indigo-carmin Test (*Mülder's*).—A solution of indigo-carmin alkalinized by sodium carbonate remains blue on boiling, but when a drop of saccharine urine is added to the hot solution, a beautiful play of colors occurs, ending in pale yellow. The test is used at present with Oliver's test-papers, charged with a definite amount of the two reagents, indigo-carmin and sodium carbonate. The papers, unless fresh, should be gently heated, dropped into a test-tube, and covered with 60 drops of water. Heat is applied until the solution is quite blue. A drop of urine is added, and the contents are boiled again. The tube is kept hot without boiling for a minute after ebullition, when the play of colors will be observed if sugar is present. Oliver claims that none of the other constituents of urine affects this test. It has also been applied to quantitative testing, as has the picric-acid-and-potash test. For ordinary work Fehling's test is sufficient and perfectly satisfactory.

Alpha-naphthol and Thymol Tests (*Molisch's*).—To 1 c.c. of the urine add 2 drops of a 15 or 20 per cent. solution of alpha-naphthol; mix and add an excess of concentrated sulphuric acid. On shaking, if sugar is present, a deep-violet color develops. On dilution with water a violet-blue precipitate is seen, which is soluble in alcohol and ether with a yellow color. If thymol is added instead of naphthol, a deep-red color is produced, and on dilution with water, a carmin-red, flocculent precipitate, soluble with a pale-yellow color in alcohol, ether, and potassium hydrate. Instead of sulphuric acid, hydrochloric acid may be used, the mixture being afterward boiled for a minute.

These reactions take place with most sugars except inosite, but not with the other reducing bodies. The trouble with these last two tests is that normal urine gives the reaction, even if diluted ten times, and they are not to be recommended unless the urine be diluted with from 300 to 400 volumes of water and the color be compared with a similar specimen of diluted normal urine.

Moore's Test.—To a small quantity of urine add half as much of potassium-hydrate solution and boil. If sugar is present, a yellowish-brown color soon appears, which becomes deeper as boiling continues, becoming almost black as the amount of sugar becomes larger. The test depends upon the fact that glucose becomes oxidized when boiled with caustic alkali. The color is due to the formation of glucic and later of melissic acids, both of which remain in solution. The flocculent precipitate which is observed after the addition of the alkali consists of earthy phosphates which, if very abundant, may be filtered off before the heat is applied. To the colored fluid a few drops of nitric acid should be added, when the brown color disappears and the odor of caramel or burnt molasses develops. The alkaline solution must not contain any lead. If the urine is high-colored, it should be decolorized by treating with acetate-of-lead solution or filtering through charcoal. A brown color with the potassium solution without heat is due to biliary coloring-matters. Moore's test is said to be sensitive to 0.3 per cent. of glucose.

QUANTITATIVE ANALYSIS OF SUGAR.

Fehling's Method.—For quantitative analysis with any method, the entire amount for twenty-four hours should be collected, measured, and a sample of the thoroughly mixed urine should be examined. The amount of sugar eliminated varies a great deal according to the time of day and the length of time after the meal. The urine should be kept as has been described in the introductory chapter, to prevent fermentation. Quantities of sugar are expressed usually in percentage, but the total number of grams of sugar eliminated must be calculated, as that is the final criterion. The severity of the disease and the result of treatment can be judged only by a comparative study of the quantity of glucose eliminated daily.

In spite of the introduction of a number of other methods, Fehling's quantitative test is still regarded as the standard. The solution, divided into two parts as described above, is to be mixed when about to be used, and the principle of the process is the same as in the qualitative method. Each 10 c.c. of Fehling's solution correspond to 0.05 gm. of sugar, or each 200 gr. to 1 gr. of sugar. The blue color disappears, and the copper is completely precipitated from a definite amount of Fehling's solution by a given amount of grape-sugar. A buret holding 25 or 50 c.c. and graduated to tenths of a cubic centimeter is filled with the urine and fastened to a buret-stand. Under this buret a Florence flask of 250 c.c. capacity is placed, on a tripod covered with a piece of copper-wire gauze, beneath which a Bunsen burner or an alcohol-lamp is placed (Fig. 10).

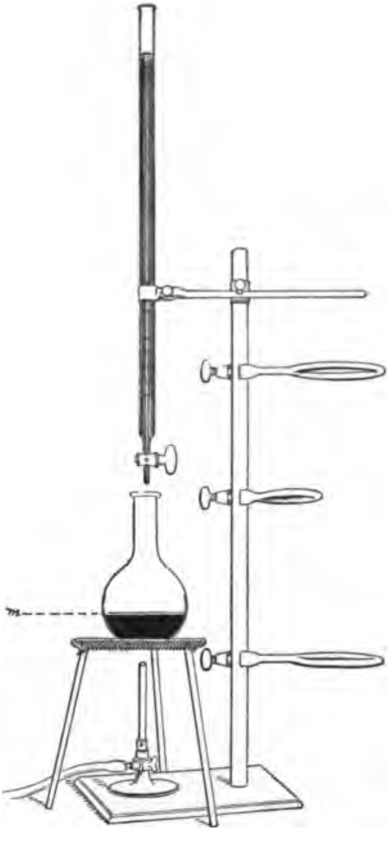


Fig. 10.—Apparatus for the quantitative estimation of sugar: *m*, Meniscus (Ogden).

The specific gravity of the urine should be tested; then the nitric-acid test for albumin should be performed, and the albumin should be removed by heat if more than a trace is present.

The removal of albumin from urine for quantitative analysis for glucose should be performed as follows:

Place 50 c.c. of the urine in a porcelain evaporating dish; add two or three drops of dilute acetic acid, and boil thoroughly. If albumin does not appear, add acetic acid, drop by drop, stirring constantly, and heating until the coagulum forms. Filter, and wash the precipitate once or twice with water. Collect the filtrate; wash in water into a graduate, and add enough water to make the original 50 c.c. Mix the contents of the graduate thoroughly, and use for quantitative tests.

If the specific gravity of the urine is over 1030, dilute it ten times with distilled water (urine 1, water 9). If less than 1030, dilute it 1:5 (urine 1, water 4). Mix the diluted urine thoroughly and pour it into the buret, filling the latter exactly to the zero mark, the lower meniscus touching this mark. It is best to fill the buret a little over the zero mark, and to allow the urine to come down to the mark by opening the stop-cock. Students who have not had much practice in titration will find it useful at first to experiment with the buret and stop-cock, so as to acquire the knack of controlling the flow and of reading the scale accurately. A buret with a black-and-white scale is useful.

Ten c.c. of each of the solutions composing Fehling's formula are measured accurately by means of a pipet and poured into the flask. Sixty c.c. of distilled water are added; the flask is placed on the wire gauze, and the mixture is boiled for two or three minutes. If the solution remains clear and does not change color, the diluted urine is added, drop by drop, from the buret into the flask, the contents of which are kept boiling. After each addition of the urine the flask should be taken up between the eye and the light and the clear line or meniscus on the surface of the fluid watched. This line is at first blue, but as the copper is reduced the fluid grows colorless and the meniscus loses all traces of blue color. When the mixture has become perfectly colorless, the number of cubic centimeters of diluted urine employed to decolorize it is read off on the buret. From this reading the percentage of sugar in the urine is calculated. Since it takes 50 mgm. (0.05 gm.) of glucose to reduce completely the copper in 20 c.c. of Fehling's solution (the amount used in the flask), the calculation will be as follows:

Example.—If 15 c.c. of diluted urine were necessary to complete the test, and if the urine was diluted 1 : 10, then 15 c.c. of this diluted urine equal 1.5 c.c. of undiluted urine. Since 1.5 c.c. of undiluted urine reduce the copper in the flask, and 50 mgm. of glucose can do the same, then 1.5 c.c. of urine must contain 50 mgm. of glucose. The percentage is obtained according to the following proportion:

$$1.5 : 0.050 :: 100 : x; \text{ hence, } x = 3.33 \text{ per cent.}$$

Suppose the total quantity of urine in twenty-four hours was 2000 c.c. Then 3.33 per cent. multiplied by 2000 and divided by 100 equals 66.6 gm., the amount of sugar in twenty-four hours.

It is important to add the urine slowly drop by drop, so as to allow the precipitate to settle after each addition. If the color disappears and again appears on standing for a short time, the blue tint is due to the reoxidation of the copper by the oxygen of the air. This should not be mistaken for an incomplete reduction. If the meniscus becomes yellow or this color is seen in the solution itself, too much urine has been added and a new estimation is necessary. The contents of the flask should be kept boiling, gently but constantly. If the solution cools, the blue color reappears from reoxidation.

Purdy's Method. - Purdy modified Fehling's method with a view of overcoming various difficulties. Take of pure cupric sulphate, 4.752 gm.; potassium hydroxid, 23.5 gm.; strong ammonia (U. S. P.), 350 c.c.; chemically pure glycerin, 38 c.c.; distilled water, to make 100 c.c. Dissolve the cupric sulphate and glycerin in 200 c.c. of distilled water with gentle heat. Dissolve the potassium hydrate in 200 c.c. of distilled water; mix the two solutions; cool; add the ammonia, and bring up the volume to 1000 c.c. with distilled water. On boiling, 35 c.c. of this solution are reduced by exactly 2 cgm. (0.02 gm.) of glucose.

Measure 35 c.c. of the solution into the flask; add about two volumes of distilled water and boil thoroughly. Fill the buret to zero with the urine, and add the latter, drop by drop, into the boiling test solution, gradually adding more slowly until the blue color disappears and the solution is left colorless and transparent. If 35 c.c. of the test solution are reduced by 2 c.c. of the urine, then 2:0.02 :: 100:x and x = 1 per cent. of sugar. If the same amount is reduced by 1 c.c. = 2 per cent.; reduced by 0.75 = 3 per cent.; reduced by 0.5 c.c. = 4 per cent.; reduced by 0.25 c.c. = 8 per cent.

It is better to dilute the urine with two volumes of distilled water and divide the product by three, as this insures accuracy of results. The advantages of Purdy's method are its clear end-reaction, the stability of the solution, and the convenience and accuracy of the test.

Whitney's Method.—A solution of ammonio-cupric sulphate, which is known as "Whitney's reagent," is prepared, so that 1 dm. of it is decolorized by $\frac{1}{30}$ gr. of glucose. One dram of the reagent is heated in a test-tube to boiling; the urine is added drop by drop, and as the color begins to fade, add more slowly, boiling for a few seconds between each addition, until the reagent is perfectly colorless, or until 10 min. have been added. If the specimen contains more than 3.33 per cent. of glucose, the urine must be diluted. The following table is given by the makers of the reagent:

If Reduced by Minims.	It Contains to the Ounce—Grains.	Percentage.
1	16.00 or more	3.33
2	8.00	1.67
3	5.33	1.11
4	4.00	0.83
5	3.20	0.67
6	2.67	0.56
7	2.29	0.48
8	2.00	0.42
9	1.78	0.37
10	1.60	0.33

Clinically this is the most rapid and convenient quantitative test for sugar, but it is the least accurate, owing to the variability of the solution and the crude technic which it involves.

Fermentation Test.—This test is very convenient for clinical use, but is not so accurate as the other quantitative methods. The most convenient method of performing it is with the aid of Einhorn's saccharometer (Figs. 11, 12).

Two sets of the apparatus are used, one with the suspected urine, the other with normal urine as a control test. A small piece of yeast, which should be fresh, is mixed thoroughly with a definite quantity of the suspected urine measured in a marked test-tube that comes with the apparatus. The mixture is then poured carefully into the graduated tube, which resembles the Doremus urea apparatus, care being taken to expel all the air by slanting the tube so that the bubbles escape. The tubes are allowed to stand at a temperature of about 86° F. until fermentation has ceased—*i. e.*, for about twenty-four hours. The carbon dioxid resulting from the fermentation collects at the top of the tube, and the percentage of sugar is read off at the level of the

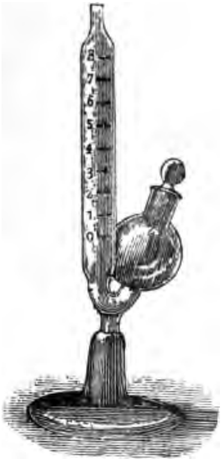


Fig. 11.—Einhorn's saccharometer.

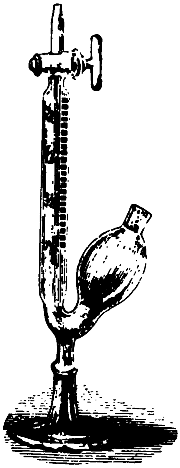


Fig. 12.—Einhorn's saccharometer with stop-cock.

fluid. If the second tube also shows a small amount of gas, this is deducted from the reading of the first tube. The results are only approximate.

Roberts' comparative density method is also approximate, but is preferred by some, as it requires no apparatus to speak of. Four ounces of the urine are placed in a twelve-ounce bottle and a piece of compressed yeast is added.* The bottle is then stoppered with a nicked cork, to allow the escape of CO_2, and set aside in a warm place. A tightly corked four-ounce bottle filled with the same urine without any yeast is placed next to it. Fermentation goes on for eighteen to twenty-four hours. The fermented urine is then decanted into a cylinder, and its specific gravity is taken. At the same time the specific gravity of the unfermented urine is also taken, and the loss of density is noted. According to Roberts, the loss of each degree of specific gravity corresponds approximately to 1 gr. of sugar to the fluidounce. Thus, if the specific gravity of the urine was 1040, and after fermentation 1020, it contained 20 gr. of sugar to the fluidounce. The two specimens of urine should be kept at exactly the same temperature.

Roberts' comparative density method may also be employed in an apparatus devised by Heinrich Stern, of New York, styled a *urinoglucosometer* (Fig. 13). This consists of a small and a large glass tube, united at their bases to form a U. The small tube is marked at 50 c.c., the large one at 100 c.c. Both are closed by means of perforated metal caps. The smaller tube is filled with urine to the mark, and is tightly closed with a rubber stopper. A small piece of compressed yeast is placed in the larger tube, and urine is added up to the mark. A urinometer is then inserted into each tube, the metal caps are put over the tubes, and the apparatus is set aside at a temperature of 80° F. for from twelve to fifteen hours. The larger tube is opened, and the contents stirred to liberate the CO_2. The flocculent mass is allowed to settle, and the cap is replaced. Then the specific gravity of the urine in both tubes is read from the flat tops of the metal caps. Each degree of specific gravity lost equals 0.2196 gm. of glucose per 100 c.c. of urine. The difference in specific gravity between the urines in the two tubes, multiplied by 0.2196, is the percentage of sugar present. The method is convenient, and though open to the objections of inaccuracy which obtain in all fermentation tests, is sufficiently exact for clinical purposes.

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* One-sixteenth of a cake of Fleischmann's compressed yeast.

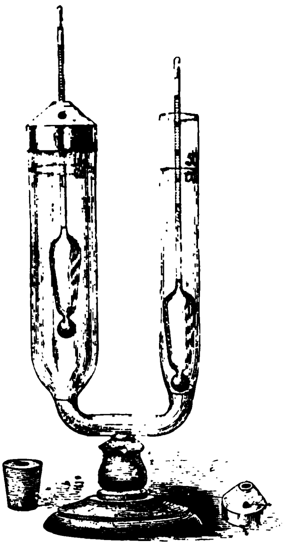

Fig. 13.—Stern's urinoglucosometer.

Schütz's Method.—An instrument devised by J. Schütz is styled an areosaccharometer, and its construction is based upon the difference in the density of urine before and after fermentation. The instrument consists of a vessel which is filled with urine and immersed in water, the long neck of the instrument being so graduated that the divisions indicate the percentage of sugar corresponding to the difference in density before and after fermentation. The vessel is filled with urine to the proper mark, and one gram of compressed yeast is added. Enough shot is put in to allow the vessel to sink to 0. The contents is shaken well and is allowed to ferment at room-temperature for from twenty-four to thirty-six hours. The instrument is then immersed in water and the specific gravity and the percentage of sugar read. This method is said to be more accurate than Einhorn's, but the latter is more convenient for every-day work.

Lohnstein's Method.—A fermentation saccharometer has been recently described by Lohnstein, which directly indicates the percentage of sugar from 0 to 10 per cent. without requiring dilution. According to a number of observers, this instrument is very accurate, but recently Rivarono, of Turin, found that comparative tests with polarimetry, Fehling's method, and Lohnstein's apparatus showed marked errors, which increased especially with the amount of albumin in the urine and the degree of dilution of the specimen.*

Lohnstein's saccharometer is intended to rectify the errors which are apt to enter in an estimation with Einhorn's apparatus, because in the latter no allowance is made for temperature, pressure, etc., as should be done in all volumetric gas analysis. Lohnstein's instrument consists of a U-shaped tube with a long arm and another ending in a bulb. Mercury is poured into this bulb up to the zero mark on the scale of the long arm. A definite quantity of urine is poured over the mercury, a little yeast is added, and the apparatus is closed with a glass stopper greased in vaselin. The stopper is weighted with lead so as to prevent the escape of any gas. The apparatus is set aside at a fixed temperature (20° or 35° C.), and the mercury rises as the gas of fermentation develops. Its level is read directly on the scale of the tube in percentage of glucose. The temperature and tension in this method remain always the same.

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* "Riforma Medica," March 30, 1904, p. 343.

The disadvantages of all the fermentation methods are their inaccuracy and the fact that they require twenty-four hours for their completion. According to Ogden, the fermentation tests yield results that are about 0.5 per cent. lower than those obtained with Fehling's method.

Polarization.—The polariscope offers the most accurate and quickest method of determining the amount of glucose when the quantity exceeds 1 per cent. The best instruments in the hands of experts can detect smaller amounts (0.01 per cent.), but, unfortunately, the apparatus is so costly that it is out of the range of the practitioner. The method depends upon the fact that glucose rotates polarized light toward the right, and that the degree of rotation varies in proportion to the percentage of sugar in the urine.

A number of polariscopes have been devised, but that of Schmidt and Haensch, of Berlin, is probably the best. It can be used with gas or petroleum light, and reads direct percentages of sugar. Although theoretically accurate for grape-sugar solutions, polarimetry is open to the objection, when used with urine, that the latter contains sometimes levu-

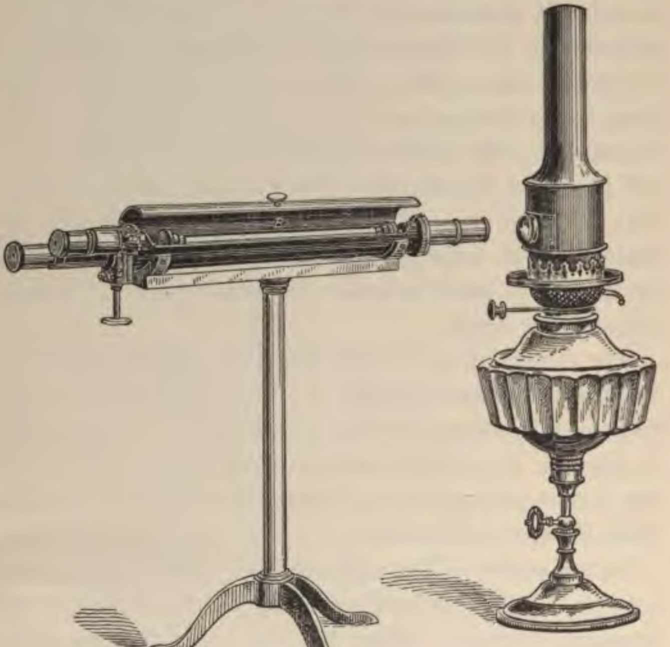

Fig. 14.—The Schmidt and Haensch polariscope.

lose, oxybutyric acid, etc., which rotate polarized light to the left.

QUESTIONS ON CHAPTER VI.

Glucose.—What does its presence in the urine indicate? What is diabetes? What other causes may produce glycosuria? What class of tests are most commonly used for searching for glucose in the urine? On what principle do they depend? Describe Trommer's test. What precautions should be taken when using any of the copper tests? Name the principal substances other than sugar which reduce copper sulphate. Describe Fehling's qualitative test. What method is used with a more stable solution? Describe the phenylhydrazin test. On what principle are the bismuth tests based? Describe Boettger's test; Brücke's modification; Nylander's test; picric-acid-and-potash test; indigo-carmin test; alpha-naphthol and thymol tests; Moore's test.

How should a sample be collected for quantitative analysis of sugar and why? Describe the apparatus used in Fehling's quantitative test. How is urine freed from albumin before this test? Describe the method of titration in Fehling's test. How is the amount of sugar calculated from the reading of the buret? What precautions should be observed in accurately determining the end-reaction in Fehling's method?

Describe Purdy's method. What are its advantages? Describe Whitney's method. What are its disadvantages? Describe the fermentation test. Describe the comparative density method for sugar. What is the polarization test for glucose and what is its value?

CHAPTER VII.

OTHER CARBOHYDRATES IN THE URINE.

LACTOSE.

Lactose (milk-sugar) is found sometimes in the normal urine of nursing women, but usually it is present in such cases in very small quantities, although Ralfe reports a case in which as much as 3 per cent. occurred. It is more apt to occur near the end of gestation, and especially in cases of mastitis. In women who have weaned their children early it is also frequently seen for a few days or a week. Lactose has no pathologic significance in urine, and is important only because it is apt to be mistaken for glucose.

Lactose ($C_{12}H_{22}O_{11} + H_2O$) is characterized by crystallization in white or colorless four-sided prisms, with acuminated ends, bounded by four triangles, and by turning polarized light to the right with a rotating power of + 59.3 degrees, while the rotation of grape-sugar is + 53.1 degrees. It reduces salts of copper, but does not undergo alcoholic fermentation with yeast. Certain cleft fungi, however, convert milk-sugar into alcohol, and ferments induce lactic-acid and butyric-acid fermentation readily with lactose. It is quite soluble in cold and freely oluble in hot water; insoluble in alcohol and ether, and precipitated by acetate of lead and ammonia.

tion is due to the levulose, it disappears; if due to the other substances, it persists after fermentation.

LAIOSE.

Laiose (Leo's sugar) was found by Leo in 1887 in some severe cases of diabetes. Laiose ($C_6H_{12}O_6$) is left-rotating, reduces copper salts, and forms a compound with phenylhydrazin. It does not ferment and is not sweet in taste. Its isolation is troublesome and of no consequence clinically, except that samples of urine that contain it show more sugar by titration than by polarization.

SUBSTANCES ALLIED TO SUGAR.

There are a number of substances closely allied to glucose which are of comparatively slight importance in urine analysis.

Inosite (*muscle-sugar*) ($C_6H_{12}O_6 + 2H_2O$) is occasionally found in conjunction with grape-sugar, and also in the last stages of chronic nephritis, in tuberculosis, syphilis, and typhus fever, as well as after drinking large quantities of water. Properly speaking, inosite is not a sugar, but should be placed among the aromatic compounds. It does not reduce the copper salts; does not ferment with yeast; is optically inactive, and does not combine with phenylhydrazin.

Its isolation and detection are cumbersome and not of sufficient clinical value to warrant further description here.

Saccharose (*cane-sugar*) ($C_{12}H_{22}O_{11}$) is very rarely found in urine, and is of no clinical importance. It has been found after eating large amounts of cane-sugar and in urines contained in a bottle that had not been properly cleaned (syrup). It is at times added to the urine by persons who wish to deceive the physician. When traces are present, they are usually overlooked. When larger amounts are present, the urine may be boiled with dilute hydrochloric and sulphuric acid, and the cane-sugar is converted into dextrose and levulose, the solution rotating light to the left, while sugar alone rotates strongly to the right. Pure saccharose does not reduce Fehling's solution.

Dextrin.—Reichard has found dextrin in the urine of diabetes instead of grape-sugar. In such cases the urine behaves with Trommer's test just like a solution of dextrin, the fluid becoming first green, then yellow, and sometimes dark brown.

Gum.—A gum-like substance has been found in the urine by Landwehr, who calls it "animal gum" and considers it a normal constituent.

Maltose.—Maltose is found occasionally in the urine in health and in disease. Von Jaksch found it in cases of malignant tumors.

Pentoses ($C_5H_{10}O_5$), in the form of arabinose, rhamnose, and xylose, have been found in the urine by Salkowski in morphin habitués, and also in diabetics by Kültz and Vogel. They are not of any clinical importance.

Glycuronic acid ($C_6H_{10}O_7$ or $CHO.(CH.OH)_4.COOH$) does not occur as such, but as a glucosid-like combination with a variety of aromatic substances of the urine, especially indoxyl, phen etc. Its chief clinical importance is that it is apt to be mistaken for glucose. Glycuronic acid is dextrorotatory, but its paired combinations, which exist in normal urine, are levorotatory, so that Haas, Johannovsky, and others found that normal urine turns polarized light slightly to the left. It reacts to the reduction tests with copper, and forms a crystalline compound with phenylhydrazin, but does not ferment with yeast.

Glycuronic acid apparently has nothing to do with diabetes. It is increased after the administration of those compounds with which it forms combinations in the urine—*i. e.*, phenol (Kültz), benzol, naphthol (Nencki), menthol, camphor, turpentine, resorcin, hydroquinon, thymol, chloral, acetanilid, curare, morphin, chloroform, etc. With these it forms fixed compounds, as naphthol-glycuronic acid, etc.

Glycuronic acid, when pure, is a syrup soluble in water and alcohol, which, on boiling with water, forms an anhydrid (lactone), glycuron ($C_6H_8O_6$), which crystallizes in colorless plates. By the action of bromin it is converted into saccharic acid ($C_6H_{10}O_8$), and is regarded as intermediate between this acid and gluconic acid ($C_6H_{12}O_7$), obtained by the oxidation of glucose with bromin (Hammarsten).

Alcapton is a substance which is rarely found in urine, both in health and in disease, and has the property of reducing copper, like glucose, without sharing the other properties of saccharine urines. It is an amorphous substance, by the reduction of which are obtained two acids, hydroquinon-acetic and uroleucinic.* It is chiefly noteworthy because it produces a dark-colored urine, which grows darker on standing, owing to the oxidation of the alcapton acids.

QUESTIONS ON CHAPTER VII.

What is the clinical significance of lactose in the urine? What are its characteristic properties? How is it detected?

What are the properties of levulose and how is it detected?

What is meant by laiose?

Name a few of the substances allied to sugar that may occur in the urine.

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* Further details will be found in Neubauer and Vogel, " Analyse des Harns," 1898, p. 243.

III. UREA AND ITS CONGENERS.

CHAPTER VIII.

UREA.

(CH_4N_2O.)

Urea is the principal nitrogenous organic constituent of urine, and is derived from the metabolism of the proteids, 95 per cent. of the total nitrogen excreted passing through the kidneys, while 5 per cent. is excreted in the feces. Urea is an index of the amount of nitrogen excreted, and, clinically, the test for the percentage of urea is the simplest method of determining the state of nitrogenous excretion. Urea, however, represents only about 85 per cent. of the total nitrogen of the urine, while 15 per cent. is represented by uric acid, the purin bodies, hippuric acid, ammonia, and creatinin.

The quantity of urea changes with the amount and composition of the food and with the rapidity of tissue-waste in health and in disease. The amount of urea excreted fluctuates at times from day to day, even in health. It is considerably increased in fever, on account of the increased breaking-down of the proteids of the body, and also in diabetes. Urea is diminished in diseases of the liver, such as acute yellow atrophy, its place being taken by leucin and tyrosin (see p. 184), and also in cirrhosis of the liver.

It is also diminished in chronic diseases accompanied by wasting and in renal diseases characterized by interstitial changes. The use of thyroid extract is often followed by an increase, the use of alcohol in children by a decrease, of urea, and a diminution has been observed in chronic alcoholism in adults.

TABLE OF VARIATIONS IN THE AMOUNT OF UREA EXCRETED.—(*After Ogden.*)

I. The Amount of Urea is Increased:

- (*a*) *Normally:*
  1. A plentiful diet of mixed character.
  2. Increased exercise.
  3. During the day as compared to the night.
  4. After the administration of ammonium compounds.
  5. After hot baths.
  6. When metabolism is temporarily increased by drinking large amounts of water or by any other means.
- (*b*) *Abnormally:*
  1. In acute fevers, owing to increased metabolism, especially in the early stages. Exceptions: Cholera and acute intestinal diseases, acute nephritis, etc., with dropsy.
  2. In dropsies when the fluid is becoming reabsorbed (temporarily).
  3. Before a chill in malaria (diminished afterward).
  4. In diabetes insipidus, urea high but specific gravity low.
  5. In diabetes mellitus, owing to increased metabolism.
  6. In chronic gout.

II. The Amount of Urea is Diminished:

- (*a*) *Normally:*
  1. With a diet poor in nitrogen (vegetarians) and in starvation.
  2. After very profuse perspiration.
  3. In normal pregnancy (often), the average being 20 gm. per twenty-four hours.
  4. After taking small doses of quinin (slightly).
  5. Prolonged drinking of large amounts of water (for a short time, urea increased).

In most diseases, especially in diminished metabolism and lowered nutrition, principally:

- (*b*) *Abnormally:*
  1. In most renal diseases, especially in the chronic forms, interstitial and parenchymatous. Not so markedly in amyloid kidney. In acute nephritis, especially when dropsy is increasing.
  2. In functional disturbances of the kidneys; congestion.
  3. In acute fevers, after the acme and during convalescence, when metabolism is low.
  4. In all dropsies while the fluid is increasing.
  5. Shortly before death; usually a marked diminution.
  6. After prolonged vomiting.
  7. With marked diarrhea, urea being partly eliminated in the feces.
  8. In all degenerative changes of the liver.

The amount of urea normally excreted with an average diet is from 20 to 40 gm. (308.6 to 617.2 gr.)

in twenty-four hours in adults, or from 1.5 to 2.5 per cent. With a milk diet or with a diet containing little nitrogen, 15 gm. a day may be excreted, while in fever 50 gm. are often found.

The usual standard amount of urea in the urine of a healthy adult is taken as 2 per cent., or 20 gm. per liter, or 10 gr. to the ounce.

Tests for Urea.—Urea (CH_4N_2O) is an isomere of ammonium cyanate, and may be prepared artificially by the action of ammonia on carbonyl chlorid, by the hydration of cyanamid, and from ammonium carbonate.

It is soluble in alcohol and water; insoluble in ether; odorless, with a salty taste and a neutral reaction in solution. It crystallizes in colorless four- or six-sided prisms with oblique angles, or in delicate, white, silky needles. On the addition of nitric acid it forms urea nitrate, which crystallizes in plates of an octahedral, hexagonal, or lozenge shape (Fig. 15). With oxalic acid it forms urea oxalate, in the form of flat or prismatic crystals. If a drop of fluid is suspected to be urine, it is placed on a glass slide, and the latter is carefully warmed over the flame and set aside to crystallize after a drop of nitric acid has been added. Crystals of nitrate of urea will form and will be recognized under the microscope. This test is facilitated by the evaporation of the urine to a more concentrated form.

Quantitative Estimation of Urea.—Approximate Estimation.—As urea is the most important solid constituent of the urine and is present in the largest amount, the specific gravity runs closely parallel to the amount of the urea, and this fact has been utilized for an approximate estimation of the amount of urea present by means of the specific gravity. This can be done only when there is no sugar present, when the albumin is less than 0.2 per cent., and when the chlorids are normal. Such a urine, with a specific gravity of 1020 to 1024 and a daily quantity of 1500 c.c. (50 oz.), will contain from 2 to 2.5 per cent. of urea. A specific gravity of 1014 would indicate 1 per cent. of urea, and of 1028 to 1030, about 3 per cent.

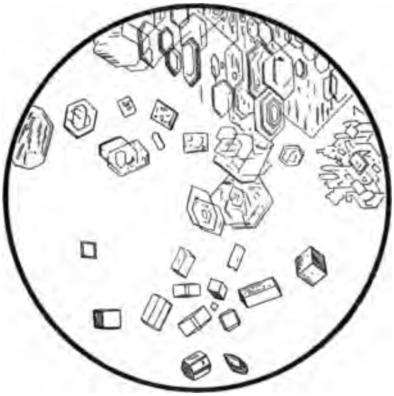

Fig. 15.—Crystals of nitrate of urea (upper half) and oxalate of urea (lower half) (after Funke).

This method, however, is very inaccurate, inasmuch as the chlorids fluctuate markedly and materially influence the specific gravity.

Hypobromite Method.—Clinically this method, introduced by Knop, is the most readily available. It depends upon the principle that urea, when brought into contact with sodium hypobromite, is decomposed into nitrogen, carbon dioxid, and water, according to the following formula:

$$CH_4N_2O + 3NaOBr = 3NaBr + CO_2 + N_2 + 2H_2O.$$

The amount of nitrogen disengaged is the measure of the urea. The carbon dioxid set free at once combines with the excess of sodium hydrate in the hypobromite solution used, forming sodium carbonate, which remains in solution. All methods of quantitative analysis of urea which involve the use of hypobromite solution depend upon the fact that 1 c.c. of nitrogen at standard temperature and pressure equals 0.0027 gm. of urea; or, conversely, that 1 gm. of urea at 0° C. furnishes 370 c.c. of nitrogen.

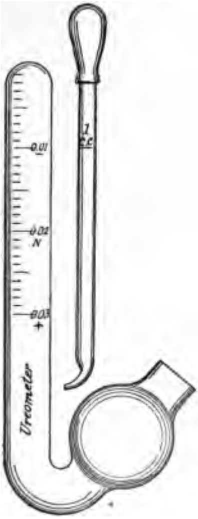

Fig. 16. — Doremus' ureometer.

Doremus' Method.—A variety of apparatus has been devised for the application of these methods of urea estimation, but Doremus' is the most useful for rapid clinical work (Fig. 16).

The apparatus consists of a bulb with an upright graduated tube, and a small nipple pipet holding 1 c.c. of urine. Each of the small divisions on the tube represents 0.001 gm. of urea. The bulb is filled with the hypobromite solution, the apparatus being inclined so as to remove the last air-bubble from the closed part of the tube. The pipet is then filled with urine accurately up to the 1-c.c. mark. The point of the pipet is introduced into the bend of the tube just as far as it will go, and the nipple is slowly and gently compressed, so as to expel all the urine, but not to expel any air out of the nipple into the gas-tube. Care should be taken after filling the pipet with urine to wipe it dry, so as to remove all the adhering urine, and also to see that no drop escapes from the point before it is introduced into the bend of the tube. The evolution of the nitrogen is allowed to proceed at the upper closed end of the tube, the apparatus being set aside until no more froth or bubbles are observed. The level of the fluid is then read upon the tube, the number of cubic centimeters of nitrogen being multiplied by 100 to obtain the percentage of urea. Two forms of this apparatus are made—one graduated to read fractions of a gram per cubic centimeter of urine, the other to read the number of grains of urea per fluidounce of urine.

In using the Doremus apparatus the urine must be free from sugar and albumin, and the instrument should be allowed to stand a sufficient length of time after it has been filled. The apparatus made with a base for support is the best.

Knop's solution of hypobromite is prepared by taking 70 c.c. of a 30 per cent. solution of sodium hydrate, diluting it with 180 c.c. of water, and then adding 5 c.c. of bromin and stirring until all the bromin has been dissolved. This solution keeps for about ten days if kept in a cool, dark place. The alkaline solution must be cold, and the bromin should be added out-of-doors or under a laboratory hood. Ammonia may be used to neutralize the irritating fumes of bromin. Another way of preparing the hypobromite solution is by dissolving 100 gm. of caustic soda in 250 c.c. of water and adding 25 c.c. of bromin.

It is always best, however, to keep a stock solution of caustic soda on hand, and to add the bromin only when the solution is required. Enough caustic-soda solution of the formula last given should be poured into a suitable bottle to fill the Doremus apparatus to a sufficient level. One gram of bromin taken with a graduated pipet is added, the bottle gently shaken after closing it with a glass stopper, and the contents poured into the Doremus tube.

Rice's solutions * for the hypobromite method offer a convenient means of obtaining the same result without the disagreeable necessity of handling pure bromin. These solutions are put up in separate bottles, one containing the alkali, the other, the bromin. Five c.c. of each of these solutions and 10 c.c. of water make up the fluid to be poured into the Doremus apparatus. These solutions keep well and are very useful for clinical work.

Hinds' modification of *Doremus' apparatus* (Fig. 17) is more accurate and convenient than the original

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* The formulas for Rice's solutions are:

(1)	Caustic soda	100 gm.
	Distilled water	250 "

(2)	Bromin	1 part
	Potassium bromid	1 "
	Water	8 parts.

form, as the urine is measured more exactly and no nitrogen is lost by escape from the bulb.

A number of other methods have been devised for the determination of urea, and may be found in the larger works on urine. Of these, Squibb's is perhaps the most commonly used, but is much more troublesome than the Doremus method. The method depends upon the same principle as that of Doremus, but can be used with either hypobromite or hypochlorite solutions (Fig. 18).

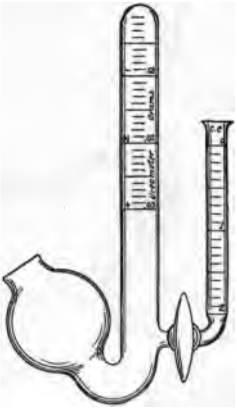


Fig. 17.—Hinds' modification of the Doremus ureometer.

Squibb's Apparatus. — This consists of two 2-ounce bottles, *a* and *b*, each supplied with a double-bored rubber stopper and connected by means of a rubber tube, *c;* a 2-c.c. pipet that is closed by a nipple; a 30-c.c. graduate *g*, into which a rubber tube *d* extends from bottle *b;* and a small glass plug, *e*. Rice's solutions, already described (5 c.c. of each), may be used in this apparatus, or the following solution of chlorinated lime: 40 gm. of chlorinated lime (chlorid of lime) are shaken with 120 c.c. of water, and after the mixture has settled, the thinner portion is poured off into a filter and filtered into a bottle marked at 200 c.c. Add 80 c.c. more of water, shake well, and pour again through the filter after the first portion has nearly all drained through. Pour water on the residue in until the filtrate reaches 200 c.c. Shake, cork, and label the bottle, dating the label. This solution keeps for a month. It gives a rapid reaction, and 10 c.c. are enough for an assay.

Process.—Bottle *a* is immersed in water at room-temperature. The rubber tube *d* is fitted on the bent-glass tube of the stopper on bottle *b*, so that it will just clear the bottom of the measuring-jar *g*, when the apparatus is in position as shown in the cut. The bottle *b* is filled with water at room-temperature, and the stopper is firmly put in place, allowing the displaced water to escape through the tubes. Then, taking the bottle in the right hand,

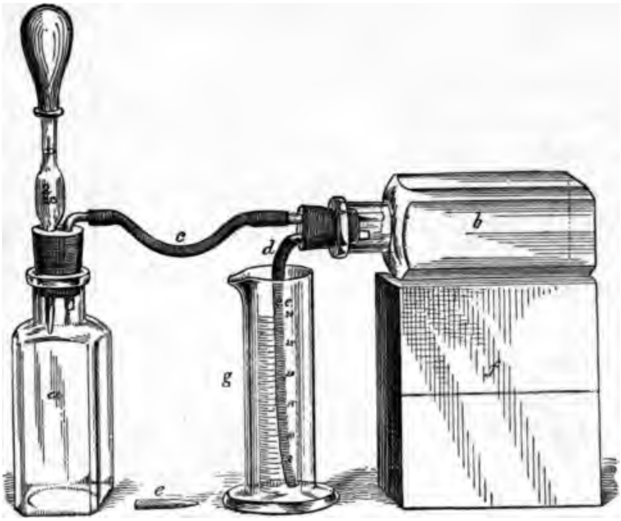


Fig. 18.—Squibb's apparatus for the approximate estimation of urea in urine.

with the forefinger closing the straight glass tube, incline the bottle toward the bent-glass tube and relax the pressure of the finger on the straight tube, so that water enough may escape to fill the tube *d* completely. Then, with the left hand, put the little glass plug *e* in the free end of *d* and lay bottle *b*, thus filled, on the lid of the box. Rubber tube *c* is connected as shown in the cut.

The amount of reagent to be used (10 c.c. of the chlorinated solution or 5 c.c. of each of Rice's without diluting the latter) is then measured in the graduate, and poured into bottle *a*, and the graduate is rinsed. The stopper of bottle *a* is dipped into water and inserted loosely in its place.

The pipet is filled with urine as exactly as possible, and the body of the pipet, being held while the point is still immersed in the urine, the rubber ring at the mouth of the bulb is screwed upward on the pipet so that the urine may rise to the mark until the lower meniscus touches the mark. Then the bulb is screwed higher still, so that a little air may enter at the tip to prevent the loss of urine. The pipet is then inserted in the stopper, and the latter is screwed firmly into place by turning the bottle. The glass plug *e* is removed from *d*, and all the water that will flow is allowed to escape. The empty measuring-jar is placed under tube *d* to receive the displaced water of the process.

Take bottle *a* by the neck and hold the upper part of the pipet ready to compress the bulb, shaking the lower part of the bottle from side to side and not up and down. Compress the bulb sc all the urine out during the shaking. During the effervescence relax the compression on the bulb gradually. The whole operation should be so gentle that not more than a drop or two will get into the rubber tube *c*. With the chlorinated solution the shaking must be continued for about six minutes, and no warm bath is needed. Bottle *a* is then immersed in the cold bath at room-temperature for about four minutes. During this immersion the contraction in bottle *a* will draw water from bottle *b* into *a*, and from the measuring-jar back into bottle *b*, and when there is no longer any change in the measuring-jar, the contraction is finished. The bottles are removed and the content of the measuring-jar is read off to 0.5 c.c. The proportion of urea is found by referring to the figures opposite the reading of the measuring-jar in the table (p. 131) furnished with each apparatus. To find the twenty-four hours' quantity of urea approximately from the percentage multiply the latter by the number of cubic centimeters voided in twenty-four hours and divide by 100. The calculation is still more accurate if, instead of percentage, we multiply the number of grams in 30 c.c. of urine by the number of cubic centimeters voided and divide by 30.

Absolute Analytic Methods.—For physiologic studies and for accurate scientific work urea is determined by more elaborate methods, which will be found described in the larger works. Of these, the Mörner-Sjöqvist method is probably the best. By the use of this method all the nitrogenous constituents of the urine except the urea and ammonia

TABLE OF APPROXIMATE PROPORTIONS OF UREA IN URINE, FOR CLINICAL USE.—(*Ogden.*)

One cubic centimeter of nitrogen gas at 0° C. (32° F.) equals 0.0027 gram of urea.

Assumed room-temperature for measurements, 18° C. (64.4° F.).

Rate of expansion, 0.003663 times the volume for each 1° C. Correction applied for 18° C. (64.4° F.) is 0.003663 × 18 = 0.0659 subtracted for each 1 c.c. as read off from the measuring jar, and the percentage is calculated from the corrected reading.

Thirty cubic centimeters are assumed as equal to one fluidounce, but in converting any considerable quantities from one measure to the other 29.52 c.c. should be taken as one fluidounce.

In converting measures to weights, and in using measures and weights together, an assumed specific gravity for abnormal urine is taken—namely, 1025 at 25° C. (77° F.); and 30 c.c. of urine of such specific gravity weigh 30.75 grams, and one fluidounce weighs 467.4 grains.

Four hundred and seventy-three cubic centimeters are assumed as equal to one pint, or sixteen fluidounces, and when these measures are used for urine, they are assumed as weighing 484.83 grams (1025 × 473) and 7478.4 grains (467.4 × 16) respectively.

The seventh and eighth columns must not be taken as having any definite relation to, or bearing upon, the assay, excepting when the total twenty-four-hour excretion amounts to just 1181 c.c., or 40 fluidounces, or very near to this measure, as the calculations are based upon this arbitrary quantity.

Reading of the Measuring Jar in c.c. (Corrected.)	Percentage of Urea.	Urea Contained in 30 c.c., or 1 Fluidounce, of Urine.		Urea Contained in 473 c.c., or 1 Pint, of Urine.		Urea Contained in 1181 c.c., or 40 Fluidounces, of Urine.		Limits Consistent with Ordinary Health in Adults. (Probable.)
		In Grams.	In Grains.	In Grams.	In Grains.	In Grams.	In Grains.	
4 c.c.	0.50	0.1538	2.34	2.425	37.44	6.055	93.60	. . .
5 "	0.63	0.1937	2.94	3.054	47.04	7.625	117.60	. . .
6 "	0.76	0.2337	3.55	3.685	56.80	9.200	142.00	. . .
7 "	0.88	0.2706	4.11	4.267	65.76	10.653	164.40	. . .
8 "	1.01	0 3106	4.72	4.897	75.52	12.227	188.80	. . .
9 "	1.13	0.3475	5.28	5.479	84.48	13.680	211.20	. . .
10 "	1.26	0.3875	5.89	6.110	94.24	15 255	235.60	. . .
11 "	1.39	0.4274	6.50	6.739	104.00	16.825	260.00	. . .
12 "	1.51	0.4643	7.06	7.321	112.96	18.278	282.40	. . .
13 "	1.64	0.5043	7.67	7 951	122.72	19.853	306.80	Lowest.
14 "	1.77	0.5443	8.27	8.582	132.32	21 427	330 80	. . .
15 "	1.89	0.5812	8.83	9.164	141.28	22.880	353.20	. . .
16 "	2.02	0.6212	9.44	9.794	151.04	24.455	377.60	. . .
17 "	2.14	0.6581	10.00	10.376	160.00	25.907	400.00	. . .
18 "	2 27	0.6980	10.61	11.005	169.76	27.478	424.40	. . .
19 "	2.40	0.7380	11.22	11.636	179.52	29.053	448.80	. . .
20 "	2.52	0.7749	11.78	12.218	188.48	30.505	471.20	Normal.
21 "	2.65	0.8149	12.39	12.849	198.24	32.080	495.60	. . .
22 "	2.77	0.8518	12.95	13.430	207.20	33.533	518.00	. . .
23 "	2.90	0.8918	13.55	14.061	216.80	35.107	542.00	. . .
24 "	3.03	0.9317	14.16	14.690	226.56	36.678	566.40	. . .
25 "	3.15	0.9686	14.72	15.272	235.52	38.131	588.80	. . .
26 "	3.28	1.0086	15.33	15.903	245.28	39 706	613.20	. . .
27 "	3.40	1.0455	15.89	16.484	254.24	41.158	635.60	Highest.

are precipitated by means of alcohol and ether after the addition of a solution of barium chlorid and barium hydrate, and finally the urea is determined in the concentrated filtrate by Kjeldahl's nitrogen method after driving off the ammonia. Kjeldahl's method consists in converting all the nitrogen of organic compounds into ammonia by the use of sulphuric acid and heat. The ammonia is distilled over and collected in standard sulphuric acid. These methods are not employed in ordinary clinical work.

QUESTIONS ON CHAPTER VIII.

Urea.—What is urea chemically? What is its physiologic significance? How does the amount of urea vary in health? in disease? What is the normal amount excreted in twenty-four hours in grains? In grams? What is the normal percentage of urea in urine? Describe a test for the presence of urea in a liquid. How can the amount of urea be approximately deduced from the specific gravity and under what conditions?

What is the principle of the hypobromite method?

Describe Doremus' apparatus. How is it used? What solution is employed? What precautions are observed in using it? What is Hinds' modification? What is Squibb's method?

CHAPTER IX.

URIC ACID AND ALLIED SUBSTANCES.

URIC ACID.

Uric acid ($C_5H_4N_4O_3$, also expressed as $\bar{U}$ or as $H_2\bar{U}$) is a nitrogenous compound formed in the body by the decomposition of the nucleins of the nuclei of the cells of the food and tissues. These nucleins are very complex in structure and contain a series of bases collectively called the alloxur, xanthin, or purin bases. E. Fisher gave the name of "purin" to a hypothetic substance from which all these bases and uric acid seem to be derived.

Pure uric acid is soluble in 16,000 parts of cold water and in 1600 parts of boiling water. Impure uric acid is more readily soluble in water. It is not acid in reaction in cold solutions when tested with litmus-paper. It is insoluble in alcohol and ether, but soluble in warm glycerin, insoluble in strong mineral acids, but soluble in alkalis. It is more soluble in solutions of urea than in water. On boiling it reduces alkaline solutions of copper, first giving a white precipitate of cuprous urate.

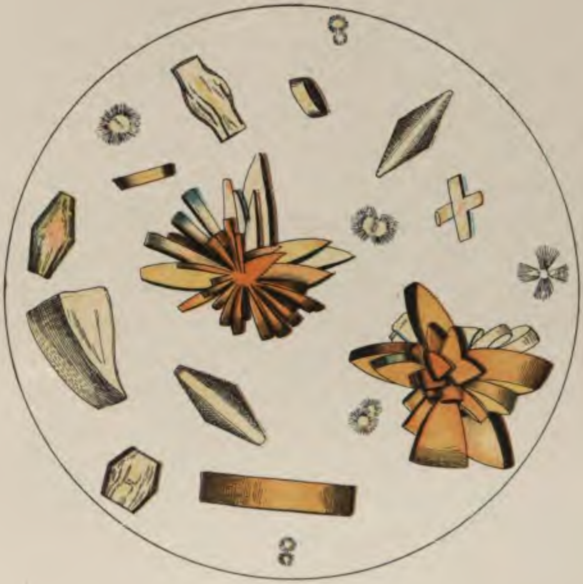
Uric acid crystallizes in the urine in rhombic, rectangular prisms, wedge- or whetstone-shaped, of a yellowish-red color (Plate 3).

The theories as to the **formation of uric acid** and as to its rôle in disease are still subjects of discussion, and some phases of this question are undoubtedly in need of revision. Until recently it was thought that uric acid was a product of nitrogenous metabolism, and was intermediate between the original food-stuffs and the final product, urea. Recent researches, however, tend to show that it is derived from the nuclei whose nucleins can be split up into an albumin and nucleic acid. Uric acid is thought to be formed from nucleic acid through the oxidation of the xanthin, alloxur, or purin groups contained in the molecule of nucleic acid. Foods rich in nuclei give rise to the formation and elimination of large quantities of uric acid. As yet, however, it is impossible to say whether or not some other constituents of the diet act as precursors in the formation of uric acid.

Two theories are held as regards the place where uric acid is formed: Garrod claims that uric acid is not only excreted, but *formed* in the kidneys, but the view generally held to-day is that it is formed in the *tissues*, especially in the *liver* and *spleen*, and merely *excreted* by the kidneys. The latter view is supported by the following facts: Uric acid is found in the blood normally and continues to be formed there after extirpation of the kidneys. It is greatest in amount during digestion, when the liver and spleen are most active, and it accumulates in the blood and tissues in gout and anemia, when the excretion is diminished.

The **relation of uric acid to gout** has been placed in a doubtful position by recent investigations. Gout has been considered for a long time to be due to the increase of uric acid in the blood, but it has been

PLATE 3



Uric-acid Crystals; Normal Color (*after Peyer*).

found recently that such an increase does not always take place. The amount of uric acid in acute gout may be high, but is more often low, and never so high as in leukemia. The amount of uric acid excreted in the urine is so variable that it is of practically little clinical importance, especially with a mixed diet. A meal composed of food rich in nuclein will increase the uric acid in the urine more than an attack of gout.

Clinical Significance.—It is important to apprehend properly what actually constitutes an increase of uric acid in the urine. A common error is to consider urine of high specific gravity, acid in reaction, which deposits uric-acid crystals and urates, as a specimen of increased elimination of uric acid. The presence of uric-acid crystals or of a deposit of urates does not by any means indicate necessarily an excess of uric acid; in fact, such deposits may occur when a urine is cooled and undergoes "acid fermentation." Urines of high concentration (in persons who drink little water, etc.) and urines of high acidity are more apt to deposit uric acid.

A *true increase* of the uric acid in the urine can be detected only by quantitative methods. While such an increase may be accompanied by a deposit of uric-acid crystals, this deposit alone is no evidence of an increased elimination of this substance.

The cause of this seemingly paradoxic fact is that under ordinary conditions nearly all the uric acid exists in the urine in combination with sodium and other bases (see Urates, p. 139) as urates. Of these salts, those known as the neutral salts are readily soluble in the urine, while others, known as the acid urates, are much less soluble. Uric acid itself is almost insoluble in urine. As a comparatively slight influence—an increase in acidity—will convert the neutral urates into the acid, or even into uric acid, it will be seen that a deposit of urates or of uric acid depends not so much upon the amount of these substances as upon the solubility of the particular types found in a urine, a solubility affected by cold and the presence of high acidity.

Normal urine contains about 0.4 to 0.8 gm. of uric acid in twenty-four hours, the average being 0.5 gm., and the normal limit 1.25 gm. The proportion of uric acid to urea is about 1 : 45.

Uric acid is *increased* in the urine: (1) By increased metabolism with diminished exercise—*i. e.*, an abundant proteid diet, containing meats with plenty of nuclei, and a sedentary life. (2) In acute fevers and most other acute diseases. (3) In rheumatism, uric-acid diathesis, and in gout *after* the attack. (4) In diseases of the lungs and heart accompanied by respiratory insufficiency (diminished oxidation)—*e.g.*, pneumonia, hydrothorax, chronic heart disease. (5) In the presence of large abdominal tumors, ascites, etc. (respiratory insufficiency). (6) In diseases of the liver and spleen. (7) In pernicious anemia and in leukemia (destruction of nuclei of leukocytes). (8) In diabetes mellitus.

Uric-acid excretion is *diminished:* (1) By a diet poor in proteids and especially in nucleins. (2) In chronic kidney diseases and other conditions diminishing the amount of urea. (3) After prolonged drinking of large amounts of water. (4) After taking large doses of quinin. (5) In gout during the attacks. (6) In chronic wasting diseases in which metabolism is lowered.

Detection.—(*a*) A few crystals of the material are placed on a slide and dissolved in dilute sodium hydrate. A drop of dilute hydrochloric acid is added under the cover-glass, and typical crystals of uric acid will form.

(*b*) *Murexid Test.*—A small quantity of the specimen is treated with nitric acid in a small porcelain dish, and gently warmed until a yellowish-red residue is left. A very small quantity of ammonia is added, when the color will change to a beautiful purple, changing to a deep blue on the addition of a little sodium hydrate. The color disappears on warming and does not reappear on evaporating. In the case of xanthin and guanin, the color returns on evaporation.

(*c*) *Silver Test.*—Uric acid is dissolved in dilute sodium carbonate and dropped upon a paper moistened with silver nitrate. A dark spot of reduced silver is produced.

(*d*) *Copper Test.*—Uric acid dissolved in dilute sodium hydrate and treated with Fehling's solution gives a precipitate of white cuprous oxid, and finally of red cuprous oxid.

Quantitative Estimation of Uric Acid.—There is no convenient clinical method for the estimation of uric acid which is at the same time accurate. The following methods are described because they are less troublesome than any others devised:

Heintz's Method.—To 200 c.c. of filtered urine free from albumin add 10 c.c. of hydrochloric acid. Allow this to stand for twenty-four hours in a cold place; collect the uric-acid crystals on previously dried and weighed filter-paper; wash once or twice in cold distilled water; dry the whole at about 100° C., cool, and weigh. By subtracting the weight of the filter-paper the weight of the uric acid in 200 c.c. of urine is obtained. This method is only approximate.

Ruhemann's Method. — In 1902 Ruhemann suggested a colorimetric method of estimating the amount of uric acid in urine based on the titration of uric acid with iodin with the aid of carbon disulphid. A graduated tube with a glass stopper, called the *uricometer*, is used for this test. One cm. above the bottom of this tube is a line marked S, and 2.7 cm. over this is another line marked J, the distance between them being divided into two by another line. Above the line J is a scale indicating parts of uric acid per 1000, beginning below at 2.45 and ending above at 0.175 (Fig. 19).

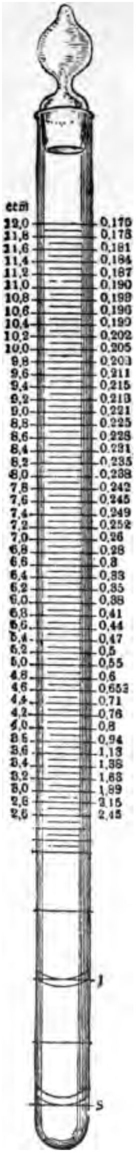


Fig. 19. — Ruhemann's uricometer.

The tube is filled to S with pure carbon disulphid, the lower meniscus touching the line. The iodin solution (iodin 1.5, potassium iodid 1.5, absolute alcohol 15, distilled water 185) is poured over this up. to the mark J, and enough urine is added to reach the mark 2.45, and then, drop by drop, closing the tube and shaking it after each addition. The carbon disulphid, absorbing the free iodin, becomes coppery-brown; the rest of the fluid assumes the color of urine. On the addition of further amounts of urine, drop by drop, the carbon disulphid become violet, pinkish violet, pink, pale pink, and finally milky white, the foam taking part in the color changes. The end-reaction is shown by a pale-pink color in the carbon disulphid. The stopper should be removed cautiously, and the foam got rid of by gently shaking the tube from side to side. The scale is read directly, showing the number of parts of uric acid per 1000 of urine, or grams per liter. If the urine has very little uric acid, then only half the amount of iodin solution should be used, the rest of the space up to J being filled with distilled water and the figures divided by two. If an excess of uric acid is present, twice the amount of iodin is used, and the result multiplied by two. The urine must be acid and free from albumin. This method has recently been found to give a considerable percentage of error, but is recommended by some clinicians.

All the other methods, such as those of Salkowski-Ludwig, Hopkins, etc., are too elaborate for clinical application.

URATES.

As has already been mentioned, nearly all the uric acid of the urine is in combination with sodium, potassium, ammonium, calcium, and magnesium, in the form of urates. These are very soluble at body-temperature, but are precipitated, on cooling the urine, in the form of amorphous granules.

Uric acid is dibasic, forming neutral and acid salts, and the acid salts are much less soluble than the neutral. They, therefore, form the bulk of the precipitate, while the neutral or less acid salts remain in solution. Urine which remains clear for some time on standing at room-temperature often contains a large proportion of the neutral urates.

When an acid is added to such urine, the urates become acid, consequently insoluble, and precipitate in a finely granular form, with the result that the urine becomes decidedly opaque. This is the cause of the opacity observed with the nitric-acid test for albumin and of the opaque zone occurring in Heller's test. Heat dispels this precipitate. If the urine mixed with acid be allowed to stand, the sediment falls to the bottom in the form of crystals of acid urates, and if the acid be allowed to act long enough, crystals of uric acid are deposited.

THE XANTHIN BASES.

We have already referred to the xanthin bases (also called nuclein bases and alloxur bases) in the section on Uric Acid. They are derivatives of the nucleins; form, with uric acid, a part of the purin bodies of E. Fischer, are present in very small quantities in normal urine, and have very little practical significance. The chief examples of this group are xanthin ($C_5H_4N_4O_2$); heteroxanthin

($C_5H_3N_4O_2.CH_3$); hypoxanthin ($C_5H_4N_4O$), and paraxanthin ($C_5H_2N_4O_2(CH_3)_2$) (Fig. 20).

NUCLEIC ACIDS.

Mörner found nucleic acids in very small quantities in the urine. Larger amounts appear in combination with albumin as nucleo-albumin. These acids are interesting physiologically, as they are compounds of phosphoric acid, xanthin bases, and non-nitrogenous substances. They may contain as much as 9 or 10 per cent. of phosphorus. They do not give the reactions of proteids, but when some of them are boiled with dilute mineral acid, a carbohydrate substance is produced which gives the reduction test with copper.

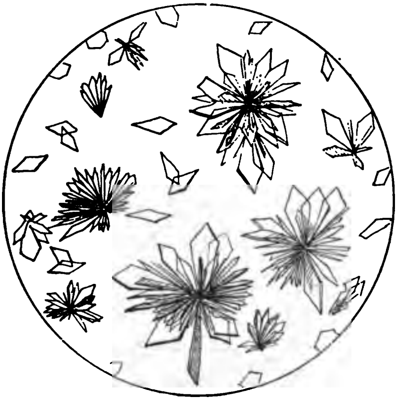


Fig. 20.—Xanthin crystals (after the drawings of Horbaczewski, as represented in Neubauer and Vogel).

QUANTITATIVE TEST FOR PURIN BODIES.

The term "purin bodies," introduced by E. Fischer, includes a series of compounds which contain the factor C_5N_4, a hypothetic body designated as "purin." We have described the principal ones, uric acid and the xanthin bases.

There are two varieties of purin bodies in the urine. The *exogenous* purin bodies are derived from the food, and vary according to the amount of food taken. The *endogenous* purin bodies are derived from the decomposition of the nucleins of the tissue-cells.

The value of the estimation of the total amount of purin bodies in the urine is, that by the use of tables showing the amount of purin in various foods, when the diet is controlled, we can know the amount of purin bodies ingested in the food, and by subtracting this from the amount found in the urine, can obtain a figure for the endogenous purins. As a comparatively simple process has been found for quantitatively testing for purin bodies in the urine, this method seems to be destined to replace the quantitative tests for uric acid, which are of no practical value, according to Hall and others, except in acute gout and leukemia. The chief value of the purin test lies in the fact that we can determine thereby not only the state of the metabolism, but also can, by varying the diet, reduce the daily amount of purins eliminated to the normal.

Camerer's Method.—An apparatus is made under the name of purinometer (Fig. 21), in which the amount of purin bodies as a whole may be approximately estimated, as follows (the apparatus consists of a graduated cylinder divided into two parts by a glass cock):

The total quantity of the urine must be known and well mixed. It is, if necessary, freed from albumin by boiling in slightly acid solution. With the tap at right angles to the tube, 20 c.c. of No. 1 solution are added to 90 c.c. of urine. The phosphates are at once precipitated, and the tap is turned parallel to the tube. In ten minutes the phosphates will have passed into the lower portion of the tube, and the tap is again turned at right angles and No. 2 solution added up to 100 c.c. The resultant precipitate of silver-purin should be pale yellow. Incline the purinometer backward and forward until all the white silver chlorid is dissolved. If this does not occur, add a few drops of strong ammonia or use diluted urine. Place the apparatus in a cupboard away from the light, and read off the number of cubic centimeters occupied by the precipitate an hour later, although it is better to wait for twenty-four hours.

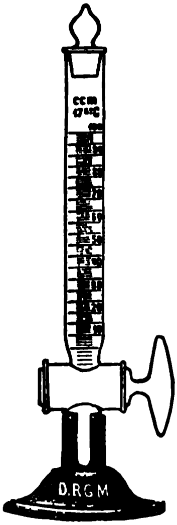


Fig. 21.—Purinometer.

Solution No. 1 *consists of:*

Ludwig's magnesia mixture*	100 c.c.
Ammonia (20 per cent.)	100 c.c.
Talcum	10 gm.

* Magnesium-chlorid crystals	100 gm.
Water	1000 c.c.

Ammonia, enough to give strong odor.
Ammonium chlorid, enough to dissolve the precipitate which forms.

Solution No. 2 consists of:

Silver nitrate	1 gm.
Ammonia, strong	100 c.c.
Talcum	5 gm.
Distilled water	100 c.c.

A table is given with the apparatus for converting the reading in cubic centimeters to the amount of purin-nitrogen in twenty-four hours.

This table shows the nitrogen percentage yielded by each cubic centimeter of the precipitate. Multiply this factor by the number of cubic centimeters contained in the twenty-four hours' urine divided by 100.

	Percentage Purin-nitrogen
4 c.c.	0.0078
5 c.c.	0.0097
6 c.c.	0.0117
7 c.c.	0.0136
8 c.c.	0.0156
9 c.c.	0.0175
10 c.c.	0.0185
11 c.c.	0.0195
12 c.c.	0.0205
13 c.c.	0.0218
14 c.c.	0.0225
15 c.c.	0.0234
16 c.c.	0.0249
17 c.c.	0.0260
18 c.c.	0.0265
19 c.c.	0.0270
20 c.c.	0.0275
21 c.c.	0.0283
22 c.c.	0.0286
23 c.c.	0.0299
24 c.c.	0.0312
25 c.c.	0.0325

Example.—The precipitate yielded 10 c.c. This contains 0.0185 nitrogen. The total daily urine was 1120 c.c.: 0.0185 × 11.2 = 0.2072 purin-nitrogen.

ALLANTOIN.

Allantoin ($C_4H_6N_4O_3$) is found in the urine of newly born infants and also in adults, but in the latter in mere traces. It is increased by meat diet, by taking tannic acid, and in cases of diabetes insipidus and hysteria.

Allantoin is obtained from uric acid by oxidation, —*e. g.*, with potassium permanganate,—and is decomposed by heat and hydrochloric acid into allanturic acid and urea:

$$\underset{\text{Allantoin}}{C_4H_6N_4O_3} + H_2O = \underset{\text{Allanturic acid}}{C_3H_4N_2O_3} + \underset{\text{Urea.}}{CH_4N_2O}$$

CREATIN AND CREATININ.

Creatin and creatinin ($C_4H_9N_3O_2$ and $C_4H_7N_3O$) are found in normal urine, creatinin containing one molecule less of water than creatin. They are both derived from muscle-tissue of the body and from meat taken as food. The amount varies according to the waste of muscle and the meat ingested. It is increased in acute diseases, such as typhoid, pneu-

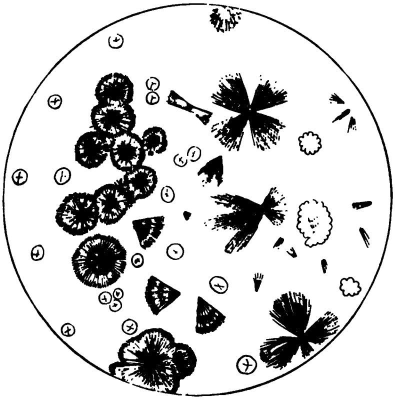


Fig. 22.—Crystals of creatinin-zinc chlorid (Salkowski).

monia, etc., and diminished in hunger and all conditions of wasting (Fig. 22).

HIPPURIC ACID.*

Hippuric acid ($C_9H_9NO_3$) occurs in normal urine of man in quantities of from 0.1 to 1 gm. in twenty-four hours, varying largely according to the amount of vegetable food. It is absent in the urine of carnivora and is very abundant in that of herbivora.

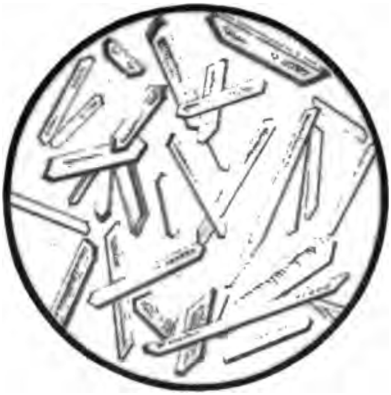


Fig. 23.—Hippuric-acid crystals (Jakob).

It crystallizes in fine needles or in four-sided prisms and pillars with ends beveled in two or four planes (Fig. 23). The typical crystals are vertical rhombic prisms. Hippuric acid is soluble in water and alcohol, and its solutions are strongly acid in reaction. It combines with alkalis and alkaline earths to form soluble salts, but its silver, copper, and lead compounds are sparingly soluble in water. Strong acids precipitate it from solutions of its salts. On boiling with an alkaline hydrate hippuric acid decomposes into benzoic acid and glycocoll. This is clinically interesting because the same decomposition takes place in alkaline fermentation, especially in urine containing albumin, so that such urine is found to contain benzoic acid instead of hippuric. Hippuric acid is probably formed in the kidneys by the union of benzoic acid and glycocoll. Clinically it has no very great significance, its amount depending chiefly upon the diet. It is increased by vegetable diet and by the use of benzoic acid, salicylic acid, and their congeners; also in acute fevers, diseases of the liver, and diabetes.

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*Hippuric acid is classified chemically as one of the aromatic group of substances in the urine. It is placed here for convenience of study

Detection.—Add concentrated nitric acid to the urine and evaporate it to dryness. The residue heated in the test-tube gives the odor of bitter almonds, due to *nitrobenzol.* When an excess is present, hippuric acid may be separated in crystals by evaporating the urine to one-fourth its volume and adding some hydrochloric acid.

QUESTIONS ON CHAPTER IX.

What is *uric acid?* From what element of the food is it derived?

What are the nucleins?

What is meant by "purin"? When is uric-acid excretion increased? Diminished?

Where is uric acid probably formed, and why is this belief now current?

What can you say of the relation of uric acid to gout?

Give the general properties of uric acid. How is it

Describe Heintz's method; Ruhemann's method.

In what form does most of the uric acid occur in urine? What two varieties of uric-acid salts occur in the urine? Which are the less soluble?

What causes the opacity observed on adding an acid to urine rich in neutral urates? How is this precipitate affected by heat?

What are the *xanthin bases?* Name some of the most important members of this group.

Describe the method of estimating the total amount of purin bodies.

What element do the *nucleic acids* contain that is of interest, and in what amount? What do these acids form when boiled with dilute mineral acids?

Under what conditions has *allantoidin* been found in the urine?

Whence are *creatin* and *creatinin* derived, and what causes their variations in urine?

What causes the variations in the amount of *hippuric acid?* What are the general properties of this acid?

Into what constituents does hippuric acid decompose on fermentation?

How is hippuric acid probably formed? When is it increased in the urine? How is it detected?

IV. ACETONE GROUP; INDICAN AND OTHER ETHEREAL SULPHATES; DIAZO-REACTION.

CHAPTER X.

ACETONE AND DIACETIC ACID.

ACETONE.

Acetone (C_3H_6O) is a volatile compound belonging to the group of ketones, and may be present in large amounts in urine in disease. In health the urine contains traces of it, especially after the use of alcohol and of food rich in proteids.

Clinical Significance.—According to von Jaksch, pathologic acetonuria occurs as follows: (1) Febrile acetonuria, in scarlet fever, typhoid, pneumonia, measles, small-pox, etc.; (2) diabetic acetonuria; (3) in certain forms of cancer, independently of inanition; (4) in starvation, especially in gastric ulcer and after the use of rectal feeding; (5) in mental diseases; (6) in auto-intoxication; (7) in derangements of digestion; (8) in chloroform narcosis.

Acetonuria is common in fevers. In diabetes its appearance shows an advanced stage, but it must be remembered that the predominance of nitrogenous food in diabetics tends to produce acetone. Cerebral irritation may give rise to persistent acetonuria.

Detection.—**Legal's test** is simple and sufficient for clinical purposes: To a small quantity of urine in a test-tube add a few drops of a strong, freshly prepared solution of sodium nitroprussid and a few drops of acetic acid (to prevent the reaction with creatinin), and then render alkaline with sodium hydrate. The presence of acetone gives rise to a red color, deepening to a purplish-red. If there is only creatinin and no acetone, the purple color does not develop. On standing, a dark-blue precipitate may form.

Lieben's Iodoform Test.—This is best applied to the distillate of the urine. Half a liter of urine is treated with phosphoric acid or hydrochloric acid in the proportion of 3 c.c. to 100 c.c. The mixture is partly evaporated into the distilling apparatus, and the process completed in a retort. The acid is added to prevent the evolution of gases. Lieben's test consists in adding a small amount of potassium-hydrate solution to the distillate, and then a few drops of a solution of iodin and potassium iodid (iodin, 1; potassium iodid, 2; distilled water, 50). Acetone, if present, gives a yellowish precipitate of iodoform at once. Alcohol gives the same precipitate, but more slowly. For this reason Gunning uses ammonium hydrate and tincture of iodin, which react only with acetone, and not with alcohol. The crystals are recognized under the microscope by their characteristic shape (flat hexagons, often arranged in star-like groups—Fig. 24), and the odor of iodoform also helps in detecting acetone.

Gunning's Iodoform Test.—This is a modification of Lieben's, designed to avoid confusion of acetone with alcohol in the urine. An alcoholic solution (tincture) of iodin and a little ammonia water are added to the distillate or to the urine itself (the latter is not so satisfactory). If alcohol is present, no precipitate will occur, while acetone produces a precipitate of iodoform and of iodin, the latter falling as a black sediment even if there be no acetone present. A large amount of acetone in the urine will cause the disappearance of the black iodin sediment after a while, but if there be little acetone, the iodin sediment is found at the bottom of the test-tube, with a layer of iodoform in yellow crystals lying over it in a thin stratum (Fig. 24). The mixture must not be warmed while there is any nitrogen iodid in it—*i. e.*, for twenty-four hours—on account of the danger of an explosion.

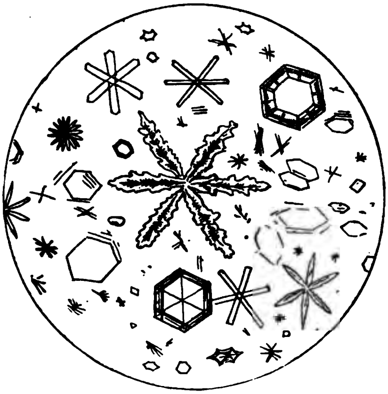

Fig. 24.—Crystals of iodoform.

Reynold's Test.—Acetone dissolves freshly precipitated mercuric oxid. Yellow mercuric oxid is precipitated from a solution of mercuric nitrate in a test-tube by the addition of an alcoholic solution of potassium hydrate. The urine is added, and the mixture shaken. The liquid is filtered until it passes through clear. To the filtrate ammonium sulphid is carefully added. If acetone is present, some mercuric oxid has been dissolved, and is shown in the filtrate by a dark ring of mercuric sulphid at the contact of the two liquids.

Bayer's and Drewsen's Indigo Test.—A few crystals of nitrobenzaldehyd are heated until dissolved, allowed to cool, the aldehyd separating as a white cloud. Add the urine, or, preferably, the distillate, and make the mixture alkaline with dilute sodium hydrate. If acetone is present, there appears a yellow color turning to green, then indigo-blue, within ten minutes. If traces of acetone are present, the yellow fluid, shaken with a few drops of chloroform, imparts a distinct blue color to the latter. This is a very delicate test.

The quantitative estimation of acetone is tedious and not clinically profitable.

DIACETIC ACID.

Diacetic acid (aceto-acetic or ethyldiacetic acid, $C_6H_{10}O_3$) is present abnormally in the urine, especially when the latter is rich in acetone. The two may exist independently, although diacetic acid is readily converted into acetone, alcohol, and carbon dioxid by the action of alkalis, a similar decomposition possibly taking place in the blood. It is a colorless liquid which gives a deep-red color with ferric chlorid.

The presence of diacetic acid is usually a serious symptom. It occurs in the urine of auto-intoxication, and especially in diabetes and in fevers. In children with fever its presence is not of grave import. In diabetes its appearance is a very bad prognostic sign. A form of auto-intoxication accompanied by diaceturia is usually rapidly fatal without any definite lesions.

Detection.—**Von Jaksch's method** is trustworthy. A solution of iron perchlorid is cautiously added to the urine. If phosphates precipitate, they are removed by filtering, and some more of the reagent is added. A characteristic Bordeaux-red color appears, but this color may be produced with the same reagent in the presence of salicylic acid, carbolic acid, and other substances. If the urine be previously boiled, diacetic acid does not give the reaction, while the other substances continue to give it. If the Bordeaux-red color develops, therefore, when a portion of the original urine is boiled, the reaction is negative.

Another portion of the urine may be acidulated with sulphuric acid and extracted with ether. If diacetic acid is present, it will be in the ethereal extract, and will give the iron reaction. If the ethereal extract pales after standing for one or two days and if the urine is found to contain large amounts of acetone, diacetic acid was present. If the color-reaction with the ethereal extract does not fad
substance is probably beta-oxybutyric

below), of which diacetic acid is a further oxidation. The urine to be tested should be perfectly fresh, as diacetic acid decomposes readily into acetone, etc., in urine on standing.*

BETA-OXYBUTYRIC ACID.

Beta-oxybutyric acid ($C_4H_8O_3$) often accompanies diacetic acid and acetone in urine. It forms an odorless, colorless, transparent syrup with aqueous vapor, and rotates polarized light to the left. It gives no reaction with ferric chlorid, but is easily convertible into acetone and diacetic acid by oxidizing.

Clinical Significance.—This substance is met with in large amounts in severe forms of diabetes and in small amounts in scurvy, scarlet fever, measles, in the starving, the insane, in cancer patients dying from coma, and in persons living exclusively on meat and fat. In diabetes it is probably the cause of the acid intoxication which usually precedes and accompanies diabetic coma. Herter found that the persistent appearance of more than 25 gm. of this acid indicates impending coma.

It is found in the blood of diabetic patients and is a homologue of lactic acid. It is formed from diseased muscle as lactic acid is from healthy, but the steps by which it is formed are unknown. Its presence in the blood has given rise to the alkaline injection treatment of severe diabetes, which is supposed to neutralize the acid in the blood.

Detection.—There is no simple reaction for this member of the acetone group. If the urine is fermented with yeast and tested for its polarity, a strong left-hand rotation indicates the probable presence of this acid. The process of isolation is tedious.

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* This process is attributed to Gerhardt by Purdy.

QUESTIONS ON CHAPTER X.

What is *acetone?* Is it present in healthy urines; if so, under what conditions? What is its significance in disease?

Describe Legal's test for acetone; Lieben's test; Gunning's test; Reynold's test; Bayer and Drewsen's test.

What is *diacetic acid* and when does it occur in the urine? What does it augur in diabetes? How is it detected?

How do we differentiate the iron reaction of diacetic acid from that of salicylic acid, etc.?

Describe *beta-oxybutyric acid.* What is its clinical significance in the urine? From what tissues is it formed?

CHAPTER XI.

INDICAN AND OTHER ETHEREAL SULPHATES; DIAZO-REACTION.

INDICAN.

Indican (indoxyl potassium sulphate; indoxyl; $C_8H_6NO\,.\,SO_2\,.\,KO$) is formed from indol (C_8H_7N), a product of intestinal putrefaction of albuminous substances. The indol is absorbed from the intestine and becomes oxidized to indoxyl (C_8H_6NO), immediately combining with potassium sulphate (and also to a slight extent with sodium), forming indoxyl potassium sulphate, which is eliminated in the urine.

Indigo-blue is formed by the oxidation of indoxyl potassium sulphate, thus:

$$\underset{\text{Indoxyl potassium sulphate.}}{2C_8H_6NKSO_4} + O_2 = \underset{\text{Indigo-blue.}}{2C_8H_5NO} = \underset{\text{Potassium hydrate sulphate.}}{2HKSO_4}.$$

Indigo-red, which has the same formula as indigo-blue, is also a product of oxidation of indican.

Clinical Significance.—Putrefaction goes on con-
ntly in the normal intestine, except in the newly
n, and so indoxyl is a constituent of normal
ne. The quantity separated from the urine as
indigo-blue is between 0.005 and 0.0025 gm. in
-four hours in normal man on a mixed diet.
diet gives very small amounts, while a liberal

meat diet, particularly of red meats, gives the largest amounts excreted in health. Diminution of indican is of no clinical importance.

Indican is increased: (1) In all diseases and conditions with increased intestinal putrefaction, especially in the small intestine. It is less marked in diseases of the colon. It is increased in typhoid fever, cholera, chronic nephritis, gastritis, acute and chronic, acute peritonitis, cancer of the peritoneum, appendicitis, diseases of the liver and pancreas, especially those with acute peritonitis, Addison's disease, lead colic, etc. It is also increased in acute diseases, such as pneumonia, pleurisy, meningitis, acute articular rheumatism, etc. (2) In any condition preventing the passage of feces through the small intestine, as tumors and other causes of obstruction. In diseases of the large intestine this increase is never seen, nor is it found in simple constipation. (3) Indican is increased also in putrefactive conditions, such as empyema, gangrene of the lungs, advanced tuberculosis with cavities, etc.

The *diagnostic value of indican*, when present in increased quantities, is considerable, yet a great deal of caution must be exercised in drawing conclusions as to the source of the indicanuria. It must be remembered that intestinal indigestion and the so-called state of "biliousness" increases indican elimination, and that a strong indican reaction is often obtained in the urine of persons accustomed to "high living," especially after overfeeding—*e. g.*, at banquets. Indicanuria is assoc vith disorders of the stomach with ease of hydrochloric acid, and the amount of indican passed varies with the hour of the day as related to meals.

Detection.—Indican is in itself a colorless substance or a brown syrup easily soluble in water, alcohol, and ether, and having a bitter taste. With acids and heat it is easily converted into indigo-blue (Heller's uroglaucin) and indigo-red (Heller's urrhodin). This conversion is the basis of the tests for indican.

Heller's Test.—This is the most convenient and practical test. Into a small conic glass or wineglass pour 4 c.c. (1 dm.) of hydrochloric acid (c. p.), and add one drop, or at most two, of pure nitric acid. The latter makes the test more delicate, but an excess of nitric acid is fatal to the test, as the oxidation will be so rapid that the reaction cannot be seen and a yellow color results. To these acids add fifteen drops of the urine and stir. Within from five to twenty minutes an amethyst color appears. Under these conditions the mixture may be colored a pale-yellowish or pinkish tint, showing that indican is diminished. A distinct amethyst color which is not intense and which appears rather slowly indicates a normal amount. A deep color appearing quickly indicates an increase of indican.

It is best to perform this test always in the same sized receptacle, and to use exactly the same proportions of urine and acids, although the quantities may be varied to suit the observer. Some definite rule should be observed always, frequently controlling oxidations with normal urine. In this way one can easily learn to distinguish increase of indican a glance.

Weber's Test.—To 30 c.c. of urine add an equal amount of hydrochloric acid and from one to three drops of dilute nitric acid, and heat to boiling. Allow to cool; add ether and shake. If indican is present, a blue froth appears on the surface, while the ether itself assumes a rose or violet color. This test is rather less satisfactory than the preceding.

Jaffé's Test.—To about 10 c.c. of urine in a large test-tube add an equal amount of fuming hydrochloric acid, and then, with constant shaking, a perfectly fresh saturated solution of calcium hypochlorite, drop by drop, until the blue color ceases to deepen. Shake with some chloroform, which dissolves the indigo, and allow to stand, the chloroform separating as a blue fluid, the color being more or less deep according to the amount of indican. Dark urines whose other coloring-matters are decomposed by hydrochloric acid and hypochlorite should first be decolorized with basic acetate-of-lead solution.

Obermeyer's Test.—The reagent is composed of strong hydrochloric acid, to which are added 2 parts per 1000 of ferric chlorid, the combination forming a fuming yellow liquid which keeps indefinitely. The urine should preferably be decolorized with a small amount of lead-acetate solution, as its pigments prevent the recognition of the blue color. Equal parts of urine and of Obermeyer's reagent are mixed in the test-tube, and about 2 c.c. of chloroform are added. The tube is corked and shaken slowly. The chloroform becomes blue in proportion to the indican present, increasing on standing. Normal urine becomes faint blue, while an increase of indican gives a deep color.

Precautions in testing for indican with any of these tests should include the removal of albumin, as the latter develops a blue color with hydrochloric acid on standing for a long time. A red color develops when iodin is present, obscuring the blue due to any indoxyl. In this case a small quantity of a strong solution of sodium hyposulphite should be added to the test-tube, and the mixture shaken. When the chloroform has settled again, the blue of the indigo will appear.

Ordinarily, indoxyl does not alter the color of fresh urine, but sometimes it may be partially or completely oxidized in the body, giving the urine a blue color, due to the deposit of indigo-blue. The same may take place outside of the body on ammoniacal decomposition. Calculi of indigo have rarely been found in the urinary tract as the result of the separation of indigo.

Rosenbach's Burgundy-red Reaction.—This is a color-reaction observed in severe intestinal disturbances in which there are a high degree of decomposition and a large amount of indican. The urine is reddish in color to start with, and on the addition of nitric acid, drop by drop, and boiling, it gives a deep, Burgundy-red color.

OTHER ETHEREAL SULPHATES.

Besides indican, there are several products of decomposition eliminated in the urine which appear in the form of sulphates of sodium and potassium.

These, together with indican, are grouped chemically as the *ethereal sulphates.* The amount of these bodies in the urine varies with the extent of putrefaction in the intestine. It is said that the best criterion of the occurrence of the amount of putrefaction in the body is the relation of the ethereal sulphates to the total sulphates, the normal proportion being about 1 to 10, the relative amount of ethereal sulphates rising as putrefaction increases. The two ethereal sulphates besides indican that are of importance are skatoxyl potassium sulphate and phenol potassium sulphate.

Skatoxyl potassium sulphate ($C_9H_8NO.SO_2K$) is formed from skatol under the same conditions as indican is from indol. It is present in the urine as a colorless compound, and when oxidized, gives a red color. When the indican test gives a purple-red color, the presence of skatol may be surmised. This red color cannot be removed by shaking the urine with chloroform, but it is extracted by amyl-alcohol. Normally it occurs in smaller quantities than indican, and clinically it is of little interest, except in connection with indoxyl.

Phenol Potassium Sulphate ($C_6H_5OSO_3.K$).—Phenol is a product of intestinal putrefaction, and is probably intermediate as to the place where it is developed between indol, which arises high up in the intestine, and skatol, which is formed low down in the tract. It is absorbed from the intestine, enters the blood, and combines with potassium sulphate to form an ethereal sulphate, phenol potassium sulphate. This is present in normal urine in amounts averaging about 0.03 gm. in twenty-four hours, and constitutes the form in which all the phenol or carbolic acid of the body exists.

Clinical Significance.—When there is an excess of indican there is usually an increased amount of phenol, but the reverse is not true. In albuminous putrefaction in other parts of the body than the intestine—as, for example, in empyema, etc.—there may be an increase of phenol alone, indican remaining normal. The use of carbolic acid, lysol, and other phenol compounds may increase the amount of phenol potassium sulphate. When phenol compounds are taken, the urine becomes smoky, dark brown or black on standing exposed to the air, as the result of the splitting-up of phenol into pyrocatechin and hydroquinon. Clinically any condition that causes increase of indican also causes an increase of phenol, especially increased putrefaction in the lower part of the small intestine and in the upper part of the large intestine.

Detection.—To detect phenol, add some nitric acid to the urine and boil, when the urine will give an odor of bitter almond oil. After cooling add some bromin water, causing a precipitate of tribromnitrophenol. To another portion of the original test add sodium hydrate to excess, and observe an orange-red color, due to the formation of sodium nitrophenol. Other tests are too elaborate, as they require the distillation of the urine.

EHRLICH'S DIAZO-REACTION.

In 1882 Ehrlich described a reaction in the urine, which has taken his name, and which depends upon the presence of certain aromatic substances which form anilin colors in the presence of diazosulphobenzol. The latter is formed by the union of sulphanilic acid (amidosulphobenzol) and HNO_2. In order to obtain a fresh solution of diazosulphobenzol, a solution of sodium nitrite is added to a solution of sulphanilic acid containing 5 per cent. of hydrochloric acid. When the two solutions are mixed, HNO_2 is set free, and diazosulphobenzol is formed. The reagents used in Ehrlich's diazo-reaction, therefore, are as follows:

Solution 1:

Sulphanilic acid	1 part
Hydrochloric acid (c. p.)	50 parts
Distilled water	1000 "

Solution 2:

Sodium nitrite	1 part
Distilled water	200 parts

The solutions should be kept in separate well-stoppered bottles of amber glass, and should be mixed when needed by combining 50 c.c. of No. 1 and 1 c.c. of No. 2. The sodium-nitrite solution does not keep well and should be prepared freshly at frequent intervals.

The test is performed by mixing equal bulks of the urine and the mixed reagents; quickly adding one-tenth volume of ammonia water, and shaking. A deep cherry-red color indicates a positive reaction, and if the reaction is marked, the foam will appear salmon-pink or even deep-red in color. On standing for twenty-four hours a green precipitate is formed which is a further proof of the true reaction.

Clinical Significance.—The chief clinical value of the diazo-test is in the diagnosis of typhoid fever. It is present very constantly in severe types of typhoid fever, with an intensity running usually parallel to the severity of the infection (Wood). The clinical value of the diazo-reaction is, however, greatly lessened by several facts:

1. It often does not occur in the milder forms of typhoid fever until the acme of the disease has been reached, and at times is wholly absent in such cases.

2. It occurs in many other diseases, notably in tuberculosis, pneumonia, pleurisy, many acute fevers (measles, scarlet fever, diphtheria, erysipelas, etc.), in syphilis, cancer, septicemia, pyemia, rheumatism, etc. In practice the chief diseases in which it puzzles the diagnostician are tuberculosis and septicemia. In pulmonary tuberculosis its presence is of bad prognostic import, and its persistence indicates an advanced stage of the disease.

3. The reaction occurs in the urine of persons who have been taking certain drugs—*e. g.*, naphthalin, chrysarobin, etc. This reaction is, however, distinguished from the true diazo-reaction by the absence of a green precipitate occurring on standing for twenty-four hours, and by the fact that the color does not disappear on the addition of acids.

Other drugs—*e. g.*, gallic and tannic acids and their compounds, iodin, and the iodids—inhibit the appearance of the reaction. This is especially to be noted in tuberculosis, where tannates are frequently given for the diarrhea.

QUESTIONS ON CHAPTER XI.

What is *indican?* How is it formed?

How is indigo-blue formed?

What is the clinical significance of indican?

What does diminution of indican imply? When is it increased?

What weight should be given to indicanuria in clinical work?

What is the principle of all indican tests? Describe Heller's test; Weber's test; Jaffé's test; Obermeyer's test.

What precautions should be taken in testing for indican?

How does indican give the urine voided a blue color?

What are indigo calculi?

What are the *other chief ethereal sulphates* besides indican in the urine?

What does the relation of ethereal sulphates to the total sulphates indicate? What is the normal proportion?

What is skatoxyl potassium sulphate? How is it detected?

What is phenol potassium sulphate? Where is it formed probably?

Why does urine containing phenol turn dark on standing exposed to the air?

What is the clinical significance of phenol potassium sulphate in urine? How is its presence detected?

Describe *Ehrlich's diazo-reaction?* On what principle is it based? What is its clinical significance? What are its limitations? In what diseases does it occur?

V. COLORING-MATTERS; BILE; BLOOD; OTHER ORGANIC CONSTITUENTS.

CHAPTER XII.

URINARY COLORING-MATTERS.

NORMAL COLORING-MATTERS.

Two pigments are always present in normal urine —*urochrome* and *hematoporphyrin*. Two other pigments—*uroerythrin* and *urobilin*—may be present, especially on standing. Urochrome gives the yellow color to the urine. Hematoporphyrin is present in small amounts, is red in color, and is considered under the head of Blood Coloring-matters. Uroerythrin gives the pink color to urate deposits, and urobilin gives urine a dark-brown color. In pathologic urines two chief groups of abnormal pigments occur, namely, the bile group and the blood group.

Urochrome is a yellow pigment which gives its natural color to urine. It is a brown, easily soluble powder, giving no definite absorption-bands when its solutions are examined with the spectroscope. It is precipitated by phosphotungstic and phosphomolybdic acids and by heavy metals. These reagents are used in decolorizing the urine, the precipitate being filtered off.

The name urochrome was first applied in 1864 by

Thudichum, and this substance is considered by some to be impure urobilin.

Urobilin ($C_{32}H_{40}N_4O_7$; urophaëin, Heller; hydrobilirubin, Maly) was first isolated by Jaffé in 1868. It has probably little to do with the color of fresh normal urine.* It is present in the urine chiefly as a chromogen,—urobilinogen,—and its color is set free only when this chromogen is decomposed. In some diseases there is an increased amount of free urobilin.

Its origin is still a subject of discussion. Two theories exist: (1) That urobilin is formed from the bilirubin that enters the intestine with the bile, through reduction by the hydrogen developed in fermentation, the reduction-product being absorbed and eliminated by the kidneys; (2) that urobilin is formed by means of oxidation in the intestine or elsewhere in the body. This is not, however, of so much importance as the fact that urobilin may be formed either from bile-pigment or from blood-pigment. Bile-pigment is formed from hemoglobin, and urobilin is increased in nearly all diseases accompanied by jaundice. *Conditions accompanied by destruction of red blood-cells give an increased amount of urobilin,* and this amount is a measure of the destruction of blood-pigment. On the average, normal urine contains 123 mgm. of urobilin in twenty-four hours, the excretion being greater in tropic climates.

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* Urobilin was regarded as the chief coloring-matter of the urine. Tyson (1895) and Purdy (1900), in their text-books, still designate it as such.

Clinical Significance.—Urobilin is increased in acute infectious diseases; acute sepsis; acute articular rheumatism; appendicitis; atrophic cirrhosis and cancer of the liver; catarrhal jaundice; lead colic; pernicious anemia; poisoning by potassium chlorate, antipyrin, etc., but is absent in phosphorus-poisoning.

Detection.—Urobilin is best detected by examining the urine directly by means of a small pocket-spectroscope. The urine may have to be diluted if it is deeply colored. The characteristic absorption-band is between the green and the blue parts, between the lines *b* and *F* (Fig. 25). These bands are rendered sharper on adding a few drops of tincture of iodin to 10 c.c. of urine.

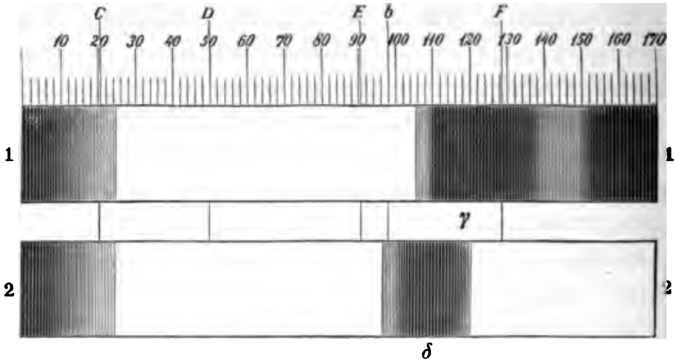

Fig. 25.—1, Acid urobilin; 2, alkaline urobilin (after Neubauer and Vogel).

When no spectroscope is available, an old test, which is very useful, the so-called *urophaëin test of Heller*, may be employed. To about 7 c.c. of concentrated sulphuric acid add twice the amount of urine in a conic glass, pouring the urine into the acid from the height of about four inches. If the amount of urobilin is normal, a garnet-red color appears, which is so intense that but little light passes through the mixture; if increased, the mixture is opaque, and if diminished, it is transparent. This test is not of any value as a specific test of urobilin, for other coloring-matters and such abnormal constituents as bile, sugar, etc., give this reaction. It is frequently used, however, as a test for urobilin after excluding the presence of sugar, bile, etc.

Harley's Test.—Dilute the twenty-four hours' urine with water until it measures 1800 c.c. (60 oz.), or, if the quantity exceed this amount, concentrate it to this measure. To four parts of it in a test-tube add one part of pure nitric acid, and allow the mixture to stand for some minutes. If the quantity of urobilin is normal, the mixture will change but slightly in color. If there is an excess, it will become pink, red, or purple according to the amount. The acid liberates the coloring-matter which may be concealed, so that a pale urine often contains a large amount of pigment.

Uroerythrin, the pigment that gives the pink color to urate deposits, is present in very small quantities and is of no practical interest. It has been termed "rosacic acid" by Prout, and "purpurin" by Golding Bird. For the most part it exists in combination with uric acid. Clinically it is increased in acute fevers and diseases of the liver, especially where there is a disturbance in the circulation, and in chronic diseases of the heart and lung. An increase of this pigment is usually accompanied by an increase in urobilin.

Uroerythrin is an amorphous substance of a brick-red color, free from iron, soluble in alcohol and very sparingly so in water. It is decomposed by oxidizing and reducing agents. It precipitates on saturating the urine with ammonium sulphate or chlorid, falling with the ammonium urate. The absorption-bands are not well defined, two in number—one between *D* and *E* and the other between *b* and *F*, the right somewhat darker than the left (Fig. 26). To get the characteristic bands, the urine is shaken with amyl-alcohol and the solution of uroerythrin thus obtained is examined. Uroerythrin is isolated by saturating the urine with ammonium chlorid.

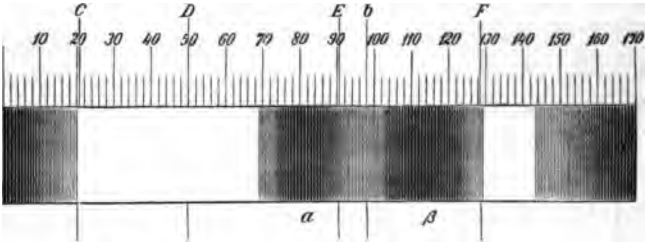

Fig. 26.—Spectrum of uroerythrin (after Neubauer and Vogel).

Urorosein does not occur in the urine as such, but as a chromogen which develops a rose-red color on the addition of acids. It is present in very small amounts in normal urine, and is increased in diseases of the lungs, pernicious anemia, severe chlorosis, diabetes, osteomalacia, typhoid, cancer, appendicitis, nephritis, diseases of the stomach, and by vegetable food.

Urorosein dissolves in water, giving a red color, also in acids, in alcohol, and in amyl-alcohol. Alcoholic solutions show a sharp and narrow absorption-band between *D* and *E*. Ammonia and fixed alkalis decolorize the red, watery solution.

Detection.—*Robin's Test.*—To 10 c.c. of the urine add 15 drops of concentrated hydrochloric acid, and if the urine be rich in urorosein, a pink color appears in about ten minutes; more quickly when the mixture is heated.

Nencki's and Siever's Test.—To 50 or 100 c.c. of the urine add from 5 to 10 c.c. of 25 per cent. sulphuric acid. A reddish or rose-red color appears in a few minutes. This colored mixture is shaken with amyl-alcohol, and the coloring-matter is removed. The extract thus made with amyl-alcohol may be evaporated, redissolved and examined with the spectroscope.

BILIARY PIGMENTS AND ACIDS.

BILE-PIGMENTS.

The presence of bile in the urine is represented by the occurrence of biliary pigments and biliary acids. Both groups will be considered here together for the sake of convenience.

Bilirubin.—Bile-pigments occur in the urine in the form of a combination of bilirubin with alkalis. When urine rich in bile-pigment is allowed to stand exposed to the air, bilirubin becomes oxidized to the green biliverdin. Bilirubin itself is orange-colored and is an intermediate product in the body between hemoglobin and urobilin. The oxidation products of bilirubin are, in the order of importance, biliverdin, already mentioned (green), bilicyanin (blue), bilifuscin, biliprasin, and choletelin.

Bilirubin occurs in a free state in urine, but the color of a bile-containing urine, though almost always abnormally deep, varies greatly between a yellowish brown to a nearly pure green, according to the presence of oxidation-products. On shaking, the froth is persistently yellow or greenish yellow. The urine permanently stains filter-paper a yellow color, and usually contains an excess of urobilin and of indican. A bile-containing urine always give a reaction for albumin, especially for nucleo-albumin, and the nitric-acid test with such urines is unsatisfactory on account of the masking of the white zone by the coloring-matter.

For this reason a urine containing much bile should be tested preferably by the *heat test*, for albumin. The sediment of such urines often contains many epithelial cells from the kidneys, casts, blood-cells, and crystals of bilirubin. The organized sediment may be stained yellow.

Clinical Significance.—Urine contains bile when there is some obstruction to the flow of bile from the liver, either in the smaller or larger biliary ducts. Bile-pigments, therefore, appear in a number of the diseases of the liver and bile-ducts, such as cirrhosis, cancer, gall-stones, catarrhal jaundice, etc. They may also appear in severe infectious diseases, phosphorus-poisoning, and other conditions in which there is a destruction of red cells. In jaundice bile-pigment often appears in the urine before the skin grows yellow.

Detection.—On inspection the urine containing bile shows the characteristics already described as regards its tint, when viewed by reflected light, and the color of its foam.

Gmelin's test consists in overlaying concentrated fuming nitric acid with the urine. A green ring appears at the point of contact; below this a blue ring, and next to this a red one. The green ring is characteristic of bile; the others may come from urobilin or from indican. At times a beautiful play of colors—green, blue, violet, red, and yellow, in the order named—is seen with this test. This test may also be applied by placing a drop of urine on a porcelain plate and allowing a drop of fuming nitric acid to mingle gradually with the urine, giving the same play of colors.

Marèchal's Test.—About a dram of an alcoholic solution of iodin of moderate strength is poured into a test-tube, and the urine is allowed to flow down the sides of the inclined tube so as to underlie the reagent. A green color appears just below the point of contact of the two fluids.

Smith-Rosin's test is the same as Marèchal's test.

Rosenbach's test is based on the fact that when a large amount of urine containing bile passes through white filter-paper, the bilirubin is retained in the paper, and when a drop of nitric acid is placed on the inner surface of the filter, a green spot is produced, changing to red.

BILE ACIDS.

Bile acids are found in the urine in the same conditions as are bile-pigments, but their determination is much more difficult than that of the pigments. According to von Leyden, the urine of hematogenous jaundice contains only bile-pigments, while that of hepatogenous jaundice contains both bile-pigments and bile acids. This is not always true, however, although the presence of a considerable amount of bile acids shows the existence of hepatogenous jaundice, while their absence does not show the absence of this form of icterus. The question as to whether bile acids occur in normal urine has not been settled.

Bile acids can be divided into two groups—the glycocholic and the taurocholic acid groups. The former are acids containing nitrogen, but no sulphur, and on the addition of water can be split into glycocoll and cholic acid. The taurocholic acids contain nitrogen and sulphur and are split into taurin and cholalic acid.

Clinical Significance.—Bile acids are present in hepatic congestion, cirrhosis, tumors of the liver, and severe acute catarrhal jaundice, anemia, scurvy, and splenic leukemia. Their clinical significance is not very important, and the tests for biliary pigments are usually sufficient to show the presence of bile without testing for the acids separately.

Detection.—Bile acids are not usually tested for in routine examinations. They must first be isolated by concentrating the urine and extracting the residue with strong alcohol, removing the alcohol by evaporation, and precipitating with basic lead acetate and a little ammonia. The precipitate is washed with ter and again extracted with warm alcohol, porated to dryness after the addition of a few drops of sodium-carbonate solution, extracting the residue for the third time with alcohol and precipitating the acids by the addition of ether to the alcoholic extract. The following test is then carried out with the precipitate:

Pettenkofer's Test.—A small amount of watery solution of bile acids is treated in a test-tube with five drops of a 10 per cent. solution of cane-sugar, and this mixture carefully layered over concentrated sulphuric acid. A red or purple ring will appear at the point of contact. The tube is dipped into cold water and shaken gently. A small amount of the purple fluid is poured into one tube, containing glacial acetic acid, and into another, containing alcohol. The spectrum of the first shows an absorption-band in green, while the second, after a few moments, becomes brown and then shows two bands, one between *D* and *E* and the other at *F*.

BLOOD-PIGMENTS.

The presence of blood in small quantities does not change the color in the urine, but larger amounts give rise to cloudiness and to a reddish sediment if the hemorrhage is recent. If the blood has been mixed with the urine for any length of time within the body, or if ammoniacal fermentation has occurred, the bloody urine is of a dirty brownish-red or dark-brown color, sometimes with a tinge of green.

The coloring-matters of the blood which occur in the urine are *hemoglobin* and its derivatives, *oxyhemoglobin*, *methemoglobin*, and *hematin*. *Hematin* is a reduced hemoglobin, and the latter is converted into hematin and a coagulated albuminous substance by means of heat. Methemoglobin is intermediate between hemoglobin and hematin. Oxyhemoglobin is obtained by shaking hemoglobin with air. These different substances are all distinguished by special absorption-bands in the spectrum.

Blood coloring-matters can enter the urine either by direct excretion by the kidney or by the disintegration of the blood-cells after they have entered the urine from different sources. The color of such urines differs according to the amount of hemoglobin or methemoglobin, the former giving a bright color, the latter a dark brownish-red. Recent hemorrhages from the larger vessels give more hemoglobin, while capillary bleeding gives more methemoglobin.

Clinical Significance.—**Hemoglobinuria** means the direct passage of the blood coloring-matters into the urine without any red blood-corpuscles. This occurs in a large variety of general diseases, such as scurvy, purpura, scarlet fever, malarial poisoning, etc. The comparative absence of blood-corpuscles and the presence of a small amount of albumin (or even the absence of albumin) distinguish hemoglobinuria from hematuria. It must be remembered, however, that blood-corpuscles are rapidly dissolved, especially in alkaline urine, and therefore that red cells may have been present in the specimen. Urine containing dissolved corpuscles is apt to be alkaline, while the urine of hemoglobinuria is acid and contains a much smaller amount of albumin. It is of lower specific gravity and deposits less sediment than the blood of hemoglobinuria.

Hematuria is a term applied to urine containing both blood-corpuscles and blood-pigments. The causes of hematuria are very numerous, for blood may come from the kidney, from the renal pelvis. from the ureter, bladder, prostate, or urethra, Blood from the kidney may be due to acute congestion, acute nephritis, or to acute exacerbations of chronic kidney disease. In acute parenchymatous and in chronic diffuse nephritis, in interstitial nephritis as the result of changes in the vessels, and in amyloid kidney hematuria is not uncommon.

Hematuria is very common in tuberculosis, tumors of the kidney, and stone in the kidney. It occurs also after the administration of certain drugs, such as turpentine, and following injuries to the kidney. In the tropics it is often caused by parasites to which allusion will be made later on (p. 300).

Bleeding from the lower urinary tract may be due to tuberculosis, stone or tumor of the bladder; acute or chronic inflammations of the bladder; traumatism; acute urethritis, urethral chancre, or surgical operations for strictures, etc. (See Table of Causes of Hematuria, p. 259.)

Relation to Albuminuria.—The presence of blood coloring-matters in very minute quantities may be observed in urines that are in every way normal. Very small amounts of hemoglobin without any albumin may be found in scarlet fever just before the onset of albuminuria, thus giving warning of the impending danger to the kidney. The blood-pigment disappears when the albumin becomes copious, and reappears as it diminishes. Hemoglobin is not found, however, in albuminuria due to fevers; as in typhoid, pneumonia, etc.

Detection of Blood-pigments.—Guaiacum Test.—Shake up equal parts of a fresh 1 per cent. alcoholic solution of guaiacum (tincture) and of turpentine that has become oxidized by long exposure to air and light. The urine to be tested is layered under this mixture, and a bluish-green and then a brilliant blue contact-ring is produced when blood-pigments are present. Pus also gives this ring, but in this case the ring disappears on heating the mixture. The blood ring, however, stays. Before using this test, an alkaline urine must be made acid. This test is very delicate.

Heller's Test.—The earthy phosphates are precipitated from the urine by means of caustic-potash solution and gentle heat. The precipitate of earthy phosphates carries with it, as it sinks, the blood coloring-matters and appears, not white, as in normal urine, but blood-red. In alkaline urine the phosphates may be precipitated by a few drops of the magnesium fluid (see p. 201) on the application of heat.

Teichmann's Hemin Crystal Test.—The precipitated earthy phosphates obtained in the preceding test are filtered out and dried on a slide. A minute granule of common salt is thoroughly mixed with the dried mixture of hematin and earthy phosphates. Any excess of salt is removed, the mixture is covered with a cover-glass, a hair is interposed, and a drop or two of glacial acetic acid is allowed to pass under the cover-glass. The slide is carefully warmed until bubbles begin to appear. On cooling, crystals of hematin hydrochlorate will form. Gentle heat only should be used in precipitating the earthy phosphates with caustic potash (see Heller's test), and the urine filtered quickly. Bubbles appearing under the cover-glass before heat is applied are carbonic acid, and should be allowed to pass away.

Spectroscopic Test.—The urine is placed in a test-tube or small trough with plate-glass sides, and examined with a small pocket-spectroscope. Water may be poured on the surface of the urine without mixing, thus obtaining a mixture graduated from pure water to pure urine. Observe the absorption-bands of oxyhemoglobin, two in number, between lines *D* and *E;* or the single line of reduced hemoglobin between *D* and *E;* or the four bands of methemoglobin, the latter giving a dark band in the red between *C* and *D* if the reaction of the urine is acid (Fig. 27).

The spectrum of hematin is rarely seen, and is difficult to distinguish from that of methemoglobin. If the urine is rendered strongly alkaline by ammonium hydrate, and if ammonium sulphid be added, the spectrum of reduced hemoglobin will appear with two bands between *D* and *E* like oxyhemoglobin, only a little nearer to the green.

Hematoporphyrin ($C_{16}H_{18}N_2O_3$), discovered in 1871 by Hoppe-Seyler, is a derivative of hemoglobin and is present in traces in normal urine. It is

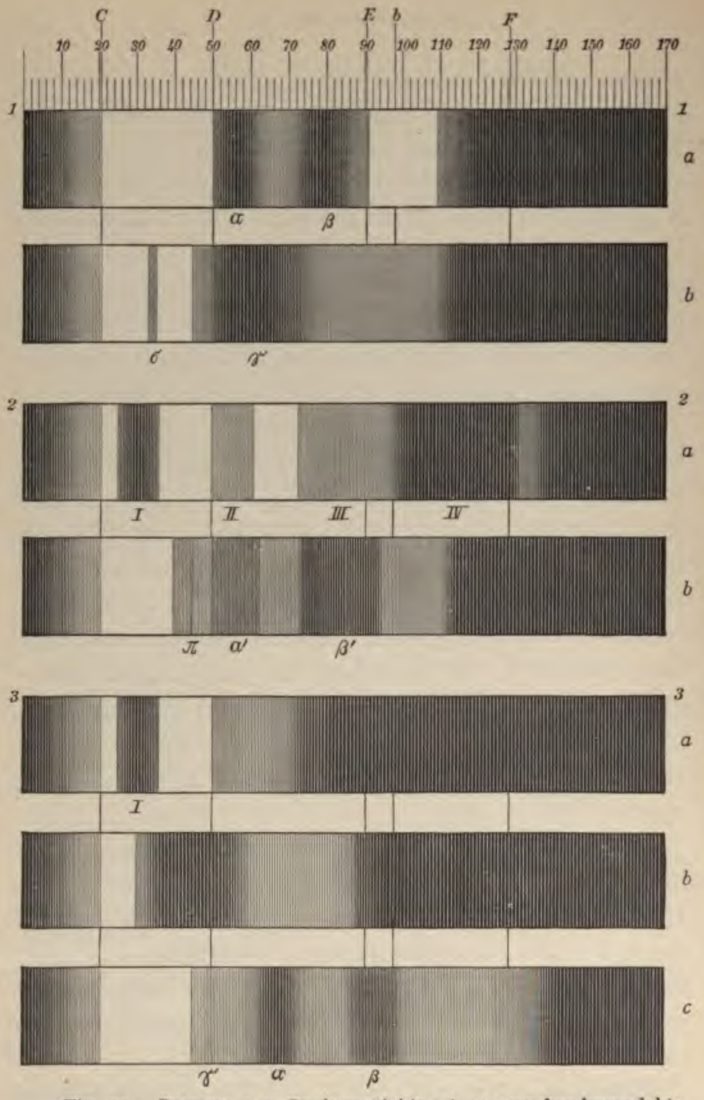

Fig. 27.—Spectra: 1 *a*, Oxyhemoglobin; *b*, oxygen-free hemoglobin. 2, Methemoglobin: *a′*, in neutral solution; *b′*, in alkaline solution. 3, Hematin in acid alcoholic solution; *b*, in ammoniacal solution; *c*, reduced hematin (after Neubauer and Vogel).

identical with iron-free hematin. A urine containing this substance is opaque and almost black, or, in a thin layer, reddish-brown. Clinically it is important when present in large amounts. It has been seen in increased quantities in leprosy, acute articular rheumatism, pulmonary tuberculosis, pleurisy with effusion, etc. It is increased by the use of large doses of sulphonal, trional, or tetronal; in lead-poisoning; in intestinal tuberculosis, and in certain nervous diseases. It can be detected only

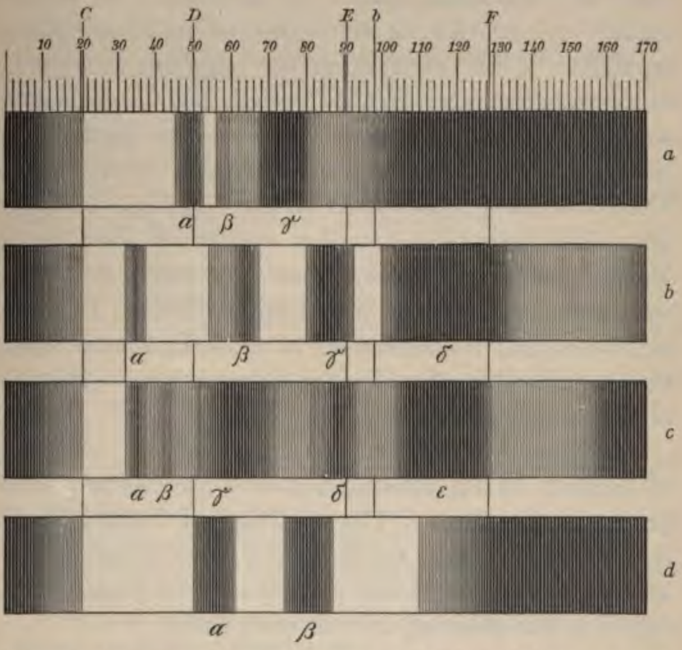

Fig. 28.—Spectrum of hematoporphyrin: *a*, Acid; *b*, alkaline; *c*, neutral; *d*, metallic spectrum.

by the spectroscope, the alkaline solution presenting a four-banded spectrum which is most characteristic (Fig. 28). Its isolation is troublesome and will be found described in the larger text-books.

Melanin is a pigment sometimes found in urine in cases of melanotic cancer or sarcoma. It occurs usually in solution of the urine or in small black particles. Urine containing this pigment is normal in appearance when freshly boiled, but on exposure to air it becomes brown or black. The pigment is eliminated in the form of a chromogen—melanogen, which becomes oxidized to melanin, probably in the liver, although this is still a matter of discussion. Melanin has also been observed very rarely in severe wasting conditions and in chronic malaria. It must be noted that melanin may be entirely absent from the urine in cases of actively progressing new growths of the melanotic type.

Detection.—*Zeller's test* consists in the addition of bromin water, causing a yellow precipitate that gradually blackens. The addition of ferric-chlorid will cause the urine to turn gray, and if enough be added, it will cause the phosphates to precipitate, carrying the coloring-matter with them.

QUESTIONS ON CHAPTER XII.

What two pigments are always present in normal urine? What two other pigments are usually present and especially on standing?

What pigment gives the yellow color to urine? the dark-brown color? the pink color to the urates?

What reagents precipitate *urochrome* and are used to decolorize urine?

In what form is *urobilin* present in normal urine?

What are the theories of origin of urobilin?

What relation does the amount of urobilin bear to the destruction of the blood-pigment in the body?

In what conditions is urobilin increased?

How is *urobilin* detected by the pocket-spectroscope? by Heller's urophaëin test? What is the value of the latter test? Describe Harley's test.

What is *uroerythrin?* When is it increased?

What is *urorosein?* When is it increased?

What is Robin's test for urorosein?

What two classes of substances represent bile in the urine?

How do *bile-pigments* occur in the urine?

What is the difference between *bilirubin* and *biliverdin?*

What are the characteristics of a bile-containing urine? What albumin test should be used in such urines, and why?

In what conditions does bile appear in the urine? Describe Gmelin's test; Maréchal's test; Rosenbach's test.

What is said of *bile acids* in jaundice?

In what conditions are bile acids present in the urine?

What is Pettenkofer's test for bile acids?

What is the appearance of urine containing fresh *blood?* Old or decomposed blood?

What coloring-matters from the blood may occur in the urine? How do they enter the urine?

What coloring-matter is found chiefly in recent hemorrhage?

Define hemoglobinuria; hematuria. How does the urine of the first differ from that of the second condition?

When does the hemoglobinuria occur?

In what diseases is hematuria seen?

What warning of an impending nephritis do we get in the urine of scarlatina?

What is the relation of albuminuria to hemoglobinuria in scarlatina? in typhoid and other fevers?

Describe the guaiacum test; Heller's test; Teichmann's test; the spectroscopic test.

What is *hematoporphyrin?* What is its clinical significance?

What is *melanin* and what does its presence imply?

What is Zeller's test for melanin?

CHAPTER XIII.

LEUCIN, TYROSIN, FATTY MATTER, AND OTHER ORGANIC CONSTITUENTS.

LEUCIN AND TYROSIN.

($C_6H_{13}NO_2$ and $C_9H_{11}NO_3$.)

These substances are products of retrograde changes of nitrogenous substances, and occur in certain fetid secretions of the skin, as in the axilla. They can be produced from the tissues of some glands, as the liver, pancreas, or spleen. They are found in the urine chiefly in diseases in the liver, especially in rapidly destructive processes, such as acute yellow atrophy or phosphorus-poisoning, and in smaller quantities in acute infectious diseases, such as typhus and small-pox. These urines always contain a large amount of biliary coloring-matter and albumin. When present in large amounts, leucin and tyrosin deposit spontaneously in the sediment. Leucin and tyrosin usually, if not always, occur together in the urine, and although some authors claim that they are present in minute traces in normal urine, their presence in any urine is very rare. The urea is very much diminished in such urines.

Detection.—If the crystals are not deposited spontaneously, the urine should be evaporated in order to display them. If this does not suffice to demonstrate them, the *method of Frerichs* may be used.

A large quantity of urine is treated with basic lead acetate, filtered, the excess of lead removed from the filtrate by sulphureted hydrogen, and the filtrate evaporated to a small volume over a water-bath. Tyrosin needles will crystallize in twenty-four hours, but leucin spheres do not appear until later, as leucin is much more soluble. If a mixture of leucin and tyrosin is extracted with alcohol, the leucin will dissolve and leave a more or less pure tyrosin. After separating the two in this way the following chemic tests may be applied:

Tests for Tyrosin.—(1) *Hoffmann's Test.*—A bright-pink or crimson color is produced when a solution of tyrosin that has been boiled in an excess of water is heated with Millon's reagent. (See p. 88.)

(2) *Piria's Test.*—Tyrosin heated with a few drops of sulphuric acid, diluted, and boiled with barium carbonate will give a filtrate which strikes a violet color on the addition of a dilute solution of ferric chlorid. An excess of iron should be avoided, as it destroys the color.

(3) A hot solution of tyrosin acidified with 1 per cent. acetic acid turns bright red on the addition of a little sodium nitrite.

(4) *Von Udránszky's Test (Furfurol).*—A small crystal of tyrosin is dissolved in 1 c.c. of water; one drop of a 0.5 per cent. solution of furfurol is added. Underlie this with concentrated sulphuric acid, keeping the temperature of the mixture at not over 50° C. The fluid is colored rose-red.

Tests for Leucin.—(1) A little leucin heated on a platinum sheet with a little nitric acid melts and forms an oily drop which rolls about on the platinum and does not adhere to it.

(2) On the addition of a trace of quinon and a few drops of sodium hydrate to a cold aqueous solution of leucin, a deep-violet color appears. (This reaction occurs also with certain proteids.)

The microscopic appearances of leucin and tyrosin crystals are characteristic and will be found described on page 245.

FAT AND CHOLESTERIN IN THE URINE.

A trace of fat is present in solution in normal urine, and abnormal quantities have been found in disease, as in cases of chronic nephritis which give fatty epithelium, fatty casts, and free oil-drops; in fatty kidney, phosphorus-poisoning, and diabetes mellitus, and in cases of cystitis and vaginitis in which fatty epithelium is present.

In *chyluria* (see p. 251) the fat in the urine is in the form of a molecular emulsion, while in *lipuria* it is present in the urine in the form of a clear fluid oil. Chylous urine may result from the leakage of a lymph-vessel into some part of the urinary tract, as in filariasis. In this disease the lymphatic vessels in the bladder-walls become filled with the embryos or mature worms of Filaria sanguinis and rupture, allowing the escape of lymph into the urine. Chyluria may occur, however, without the presence of these parasites and without definite cause. Fat in the form of oil has been found in the urine in pregnancy, fractures of the long bones, eclampsia, diabetes, pulmonary tuberculosis, and after large doses of cod-liver oil (Roberts); in cystic cheesy degeneration of the kidney; in abscesses communicating with the ureter; in heart disease, and in calculous disease of the pancreas. The admixture of fat from lubricants of catheters or from fatty material used in the vagina for examinations must not be mistaken for fat in the urine.

Cholesterin ($C_{26}H_{44}O$) is a monatomic alcohol, normally present in bile, blood-corpuscles, nerve tissues, and elsewhere in the body. In disease it occurs in gall-stones, in pus, in tuberculous and cheesy masses, in old transudates, tumors, etc. It may be present in urine under pathologic conditions, in such cases as cheesy cystic kidney, but this is of very rare occurrence. Extensive fatty degeneration of some part of the urinary tract, as subacute or chronic nephritis or the fatty stage of acute nephritis, may rarely give cholesterin crystals in the urinary

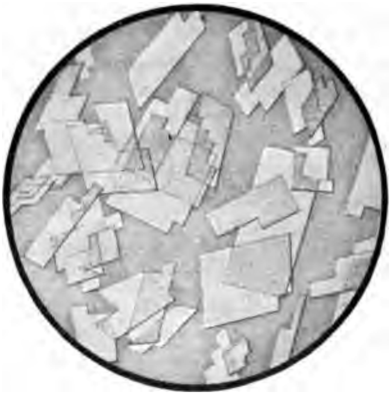

Fig. 29.—Cholesterin crystals (Jakob).

sediment. Cholesterin crystallizes in large plates, the appearance of which is characteristic (Fig. 29). It is insoluble in water, but readily soluble in alcohol, ether, chloroform, etc. Cholesterin is detected by means of the microscope.

OTHER ORGANIC CONSTITUENTS OF MINOR IMPORTANCE.

Besides the organic substances already described, very small amounts of a number of organic bodies may occur in normal urine and are sometimes increased pathologically. They may be divided into five groups: (*a*) The non-nitrogenous organic acids, *e. g.*, oxalic, lactic, succinic, etc. (*b*) The fatty acids, including formic, acetic, butyric, and propionic. (*c*) The aromatic oxyacids—hydroparacumaric and paraoxyphenylacetic, etc. (*d*) Aromatic substances present as ethereal sulphates, *e. g.*, phenol, etc. (*e*) Ferments.

Oxalic acid ($C_2H_2O_4$) is probably present in very small quantities in normal urine. Whenever there is an interference with oxidation in the body, as in diabetes, diseases of the liver, heart, or lungs, it may be increased.

Most of the oxalic acid in the urine exists as *calcium oxalate*, a salt that crystallizes and is deposited in the urinary sediment when it is present in excess. The crystals are described on page 240, where the subject of oxaluria is further discussed.

Lactic acid ($C_3H_6O_3$) is not found in normal urine, but its salts have been found in advanced disease of the liver (acute yellow atrophy, cirrhosis), in phosphorus-poisoning, in diseases of the muscles (trichinosis), and after severe muscular efforts. In the latter case it occurs in the form of sarcolactic acid. The detection of lactic acid will be found described in the larger text-books.

Succinic acid ($C_4H_6O_4$) has been found at times in normal urine, usually in combination with sodium. It is increased by eating asparagus.

Glycerophosphoric Acid ($C_3H_7O_3.PO(OH)_2$).—A portion of the phosphoric acid which is present in the urine in organic combination is contained in the nucleic acid of this fluid. (See p. 141.) It is said by some authors (Sotnitschewsky, 1880) that another portion of the organic phosphoric acid is present as glycerophosphoric acid. The amount of phosphoric acid united to organic compounds in the urine is one per cent. of the total phosphoric acid, according to Lépine, Eymonet, and Aubert (1884). Glycerophosphoric acid is a dibasic substance, syrupy in consistence, and forms salts soluble in water.

Benzoic acid ($C_7H_6O_2$) has been at times found in normal urine, and is interesting as the mother-substance of hippuric acid (*q. v.*). It is increased by the ingestion of benzoic acid or benzoates, etc., and in decomposing urine it is derived from hippuric acid. In the human body, according to Baumann, benzoic acid is formed from the decomposition of proteids in the intestine.

Chondroitin-sulphuric acid ($C_{18}H_{35}NO_{13}$-SO_3.OH) was found constantly in normal urine by Mörner (1895). This substance has been mentioned when speaking of nucleo-albumin (p. 84). Mörner considers the substance described as nucleo-albumin as a compound of a proteid with chondroitin-sulphuric acid, and also with nucleic and taurocholic acids, the latter being present especially in urine of jaundice.

Oxyproteic acid ($C_{43}H_{82}N_{14}SO_{31}$) is regarded as an intermediate oxidation-product of the proteids and is said to be a normal constituent of human urine (Töpfer, Bondzynsky, and Gottlieb).

Sulphocyanic acid (CN.SH.); **Hydrogen Sulphocyanid.**—According to Gscheidlen, sulphocyanids occur in normal urine as constant constituents, 0.035 gm. of potassium sulphocyanid being found per liter.

Volatile Fatty Acids.—Traces of acetic, butyric, formic, and propionic acids have been found in the urine. The amounts grow larger during alkaline fermentation, and are increased in some diseases of the liver; in fevers; in diabetes (von Jaksch). They have no special clinical significance, and are produced by the same conditions that cause acetonuria. Von Jaksch gave the name *lipaciduria* to the presence of an increased amount of volatile fatty acids.

Aromatic oxyacids.—Normal urine contains small amounts of hydroparacumaric and paraoxyphenylacetic acid in the form of potassium salts. These substances are probably products of intestinal proteid decomposition, and occur in larger amounts whenever indican is increased. Paraoxyphenylglycolic and oxyamygdalic acids are two other substances of the same class (Huppert) that have been found in the urine, and still another set of acids of this sort are uroleucic and homogentisic (Kirk, Baumann and Wolkoff), which constitute *alcapton*, described separately on page 118, on account of its more marked clinical significance.

Aromatic Substances.—A series of aromatic substances occurring in the urine in combination with sulphuric acid are phenol (carbolic acid), parakresol, pyrocatechin, and hydroquinon.

Phenol has been found in ileus, peritonitis (Salkowski), diphtheria, scarlet fever, and erysipelas (Brieger) in increased quantities. Phenol is said to be increased in the urine in all conditions of albuminous putrefaction in the intestine; in cholera, pulmonary gangrene, fetid pleurisy, etc.

Pyrocatechin is said to occur very frequently in urine. These urines are light colored when passed, but become dark on standing or on the addition of KOH solution. *Hydroquinon* occurs in urine after carbolic-acid poisoning, giving the urine its dark color. It is present as an ethereal sulphate.

There are methods for the isolation and quantitative estimation of all these ingredients (von Jaksch), but these are too complex and not sufficiently important to be described here.

Ferments.—Pepsin and trypsin have been found in urine. Leo found that normal urine possesses digestive powers for fibrin, and Neumeister has shown that true pepsin occurs in urine. Trypsin has been found by Sahli, though its presence is doubted by some authors.

Accidental Organic Constituents.—There are a large number of organic substances which may be present in urine when they are taken internally or absorbed from the skin or mucous membranes. The discussion of these belongs properly to pharmacology and toxicology, but a few of the more important ones may be mentioned: alcohol, glycerin, chloroform, chloral, iodoform, sulphonal, salicylic acid, salol, resorcin, guaiacol, thymol, naphthol, copaiba, santonin, aloin, phenacetin, acetanilid, antipyrin, quinin, morphin, etc.

QUESTIONS ON CHAPTER XIII.

What are *leucin* and *tyrosin*? When are these substances found in the urine? What is their relation to the occurrence of albumin, and of biliary pigments and of urea in the urine? What is the frequency of their presence in urine? How may the crystals be obtained? Which crystallizes first? How do we separate the two by means of a solvent? What is Hoffmann's test? Piria's test? the furfurol test? What is the platinum-foil test for leucin?

In what form does *fat* occur in the urine? What is lipuria?

What is *chyluria* and what is it due to?

In what conditions has fat in the form of oil-globules been found in the urine?

What extraneous fat must be guarded against in urinary examination?

What is *cholesterin?* Under what conditions may it be present in the urine? What are its properties and how is it detected?

Name some of the organic acids present in urine.

Where has phenol been found increased in the urine? Where pyrocatechin? What ferments occur in urine?

B. INORGANIC CONSTITUENTS.

The principal inorganic constituents of the urine are the chlorids, phosphates, and sulphates occurring in combination with sodium, potassium, ammonium, calcium, and magnesium. There are also traces of carbonates of the alkalis, and also minute quantities of iron, fluorin, and silicic acid, as well as free gases, including carbonic acid, nitrogen, and oxygen. The total amount of inorganic substances excreted in twenty-four hours is between 9 and 25 grams.

CHAPTER XIV.

CHLORIDS.

The chlorids, next to urea, are the chief solid constituents of the urine. Most of the chlorin in the urine exists as sodium chlorid, and small amounts are combined with potassium and ammonium. The chlorids in the urine are derived from the food, and most of the salt ingested is eliminated in the urine as such. Normally, between 10 and 20 gm. of NaCl are excreted in twenty-four hours, but if salty food is eaten, the amount may reach 40 to 50 gm. In starvation the chlorids almost entirely disappear from the urine. The tissues need a certain amount of sodium chlorid, and if salt-containing food is given after a period of starvation, some of the salt is retained in the body until the tissue fluids have enough NaCl, when the original equilibrium is restored. An increased excretion of chlorids takes place when large amounts of water are taken. An increased amount of chlorids is of no importance if it is due to an abundance of salt in the food, but in diabetes insipidus this increase takes place at the expense of the body-fluids and is associated with marked emaciation. A diminution in the amount of chlorids may be due to a diminished amount of salt in the food, and in such cases is of no importance.

Clinical Significance.—The chlorids are *diminished* in all acute diseases, especially those in which there is a serous exudation or transudation (dropsy), vomiting, or diarrhea.

The test for chlorids is, therefore, often of considerable clinical value in determining the progress of an *exudative process* or of an *effusion* into one of the serous cavities. In pneumonia the chlorids are very low or even absent in the acute stage, but as the exudate becomes absorbed and convalescence sets in, the chlorids increase and may exceed the normal for a time. In differentiating between acute meningitis and typhoid fever this test is also useful, as the serous exudation in acute meningitis causes a marked diminution in the chlorids, while in typhoid these are only moderately diminished. Other acute diseases in which chlorids are diminished or absent are cholera, septicemia, pyemia, puerperal fever, and acute articular rheumatism. In chronic diseases accompanied by dropsy chlorids may be absent from the urine, and if the fluid be absorbed, they gradually rise to near the normal. When there is no exudation or transudation in chronic diseases, the amount of chlorids is in proportion to the amount of salt in the food—*i. e.*, the amount of chlorids is a measure of the appetite. In nephritis the amount of chlorid eliminated as compared with the amount of urea is of considerable importance, as will be seen in the chapter on the Functional State of the Kidney. (See p. 346.)

Detection.—Silver-nitrate Test.—Before applying this test, if more than a trace of albumin is present, it should be removed by heat, as albuminate of silver forms and interferes with the reaction. One-half a wineglassful of urine is laid upon an equal amount of pure nitric acid in the same manner as in the test for albumin. (See p. 57.) Then one drop of a 1 : 8 solution of silver nitrate in water is added. A precipitate of silver chlorid is formed which, if normal or increased in amount, appears as a compact solid mass which falls to the surface of the nitric acid. If the amount is diminished, the silver chlorid becomes more or less diffused through the layer of urine. The same test may be applied by acidulating the urine in a test-tube with nitric acid, shaking, and adding a drop of the silver solution. A solid flocculent mass of precipitate falling rapidly indicates normal or increased chlorid; a diffused cloudy precipitate indicates a diminution. The addition of nitric acid is necessary to prevent the formation of silver phosphate.

Quantitative Test.—If a more accurate determination is wanted, Mohr's titration method with silver nitrate should be used. The solutions required are: (1) A cold saturated solution of neutral potassium chromate, made by dissolving one part of this salt in five parts of water. (2) A standard silver-nitrate solution: Dissolve 29.075 gm. of fused silver nitrate in distilled water, and add enough of the water to make exactly 1 liter (1000 c.c.); 1 c.c. of this solution is equivalent to 0.01 gm. of NaCl, or to 0.006065 gm. of chlorin.

Take 10 c.c. of urine; dilute with 50 c.c. of distilled water; add 8 or 10 drops of potassium-chromate solution, and to this mixture add the standard silver solution drop by drop from a buret. The chlorin combines with the silver to form a white precipitate of silver chlorid. When all the chlorin is precipitated, silver chromate, red in color, forms. The silver-nitrate solution must, therefore, be added until a pink tinge appears. As each drop falls into the urine it must be carefully watched for the least tinge of red surrounding the precipitate of silver chlorid. The very next drop after the complete decomposition of the chlorids—the end-reaction—gives a permanent red color to the precipitate, due to the presence of silver chromate. The number of cubic centimeters of $AgNO_3$ consumed multiplied by 0.01 will give the amount of chlorids estimated as NaCl in 10 c.c. of urine, whence the total for twenty-four hours is calculated. One c.c. should be deducted from the reading of the buret for correction. To calculate the amount of chlorin multiply the corrected reading by 0.006065, giving the amount of chlorin in 10 c.c. of the urine used.

Albumin should be removed by heat, and alkaline urine should be acidulated with acetic acid before testing. A highly colored urine gives rise to difficulty in detecting the end-reaction, and should be diluted to a greater extent. A pale urine may be diluted to a lesser extent. The correction, subtracting 1 c.c. from the reading of the buret, is necessary because the urine contains certain compounds more easily precipitated than silver chromate. The reading is, therefore, not absolutely accurate, and modifications of Mohr's process have been devised for the purpose of obviating this error. These methods are described in the larger text-books.

Purdy's Centrifuge Method.—This has been described in general under the heading of Albumin Tests. The percentage tubes of the apparatus are filled to the 10-c.c. mark with the urine. From 15 to 30 drops of nitric acid are added to prevent the precipitation of silver phosphate, the amount of acid varying with the specific gravity of the urine (the higher the latter, the more acid is used), and the tubes are filled to the 15-c.c. mark with the solution of silver nitrate. The tubes are closed and the contents thoroughly mixed. The tubes are placed in the centrifuge and revolved at the rate of 1000 revolutions a minute for three successive periods of five minutes each, when the quantity of bulk-percentage is read off on the scale of the tube. This bulk-percentage in normal urine ranges from 10 to 12 per cent. Each one-tenth of a cubic centimeter of the precipitate calculated as chlorin is equivalent to 0.123 per cent. by weight.

QUESTIONS ON CHAPTER XIV.

What are the principal classes of inorganic constituents in the urine?

What inorganic substances occur in minute quantities?

What gases occur in the urine?

What is the chief group of solids in the urine next to urea?

Whence are the *chlorids* of the urine derived?

How much NaCl is eliminated normally in twenty-four hours?

What effect has starvation upon sodium-chlorid elimination? Increased amounts of water drunk?

What does increase of chlorids mean in diabetes insipidus?

When are chlorids diminished? Of what value is this in diagnosis?

How does dropsy affect the amount of chlorids? Absorption of dropsical fluid?

How are the chlorids estimated approximately? How are they determined accurately?

Describe Purdy's centrifuge method for the estimation of chlorids.

CHAPTER XV.

PHOSPHATES.

Phosphoric acid in the urine is present in the form of two varieties of phosphates: (1) *Earthy* phosphates, or phosphates of calcium and magnesium, the former being the more abundant; (2) *alkaline* phosphates, or phosphates of sodium and potassium, the former being present in larger quantities.

Earthy phosphates are insoluble in water, but soluble in acids. In acid urines they occur as *acid* phosphates in solution, although occasionally a faint precipitate of acid calcium phosphate ($CaHPO_4 + 2H_2O$) is seen in acid urines. When urine becomes alkaline the acid phosphates are converted into *normal* phosphates and precipitate as a heavy, amorphous, whitish sediment. On heating a faintly acid, neutral, or alkaline urine (see Albumin Tests) a similar precipitate is often obtained, because this converts the acid phosphates into normal phosphates, which are precipitated, and into superphosphates, which remain in solution.

$$4CaHPO_4 = CaH_42PO + Ca_32PO_4.$$

The addition of a few drops of acid quickly dissolves the earthy phosphate precipitate. When ammoniacal fermentation occurs, the ammonia combines with the magnesium phosphate to form ammoniomagnesium phosphate or "triple phosphate." (See Description of Crystals, p. 243.)

Alkaline phosphates are soluble in water and alkalis. The sodium compound is chiefly responsible for the acidity of the urine (monosodic acid phosphate, NaH_2PO_4). The alkaline phosphates are more abundant in the urine than the earthy, the proportions being sometimes as two is to one.

Clinical Significance.—The phosphates in the urine are derived partly from the food and partly from the decomposition of organic substances containing phosphorus, such as nuclein and lecithin. The average amount excreted in twenty-four hours, calculated as phosphoric anhydrid (P_2O_5), is from 2.5 to 3.5 gm., depending, in health, upon the diet. With a diet rich in earthy salts the phosphoric acid may combine with the earthy salts and thus fail to be absorbed.

In disease phosphoric acid *is increased* in rickets, osteomalacia, and other changes in the bones; in destructive diseases of the lungs (tuberculosis) and of the nervous system; and in diseases of the brain, as well as in acute yellow atrophy of the liver. Phosphates are temporarily increased by drinking large amounts of water and after sleep induced by bromids or chloral.

By *phosphaturia* is meant an increase in the total amount of phosphoric acid in the urine, and this term should not be applied to urine that merely has a deposit of phosphates. As has been stated before (p. 198), such deposits are usually due to the diminished acidity of the urine, resulting in a lessening of the solubility of the phosphates. Some writers speak of *phosphatic diabetes* in which there is no sugar in the urine, but a constant excess of phosphates, while clinically there is a set of symptoms much like those of diabetes. This condition has been known to alternate with diabetes itself.

Phosphoric acid *is diminished* in a variety of acute diseases, probably on account of the small amount of food ingested; in most chronic diseases (except those mentioned above, in which it is increased); in diseases of the kidney; in gout; in pregnancy, owing to the formation of the bones of the fetus; and after the administration of large amounts of lime salts, ether, or alcohol.

Detection.—Earthy Phosphates.—Render half a test-tube full of filtered urine alkaline with ammonia, and warm gently, causing the precipitation of earthy phosphates in the form of a whitish cloud that settles to the bottom of the tube. The precipitate is dissolved on the addition of acetic acid.

This test may be also made to serve approximately for quantitative estimation, according to Ultzmann: A test-tube 2 cm. wide is filled with the urine to the depth of 5⅔ cm., and a few drops of strong ammonia are added. The mixture is warmed over an alcohol lamp until the earthy phosphates separate. The depth of the sediment is measured after standing for fifteen minutes. Normally, the layer will be 1 cm. high; a greater depth indicates an increase, while a less abundant precipitate means diminution.

Alkaline Phosphates.—After the earthy phosphates have been separated as shown above, the mixture is filtered. To the filtrate add one-third of its volume of magnesium fluid (magnesium sulphate, ammonium hydrate, ammonium chlorid, of each, one part; water, eight parts). The white precipitate consists of alkaline phosphates. To make this test available for approximate estimation, according to Ultzmann, 10 c.c. of the urine are treated with 3 c.c. of the magnesium fluid. A precipitate of crystalline ammoniomagnesium phosphate is formed, together with an amorphous mass of calcium phosphate. If a milky turbidity permeates the entire fluid, the alkaline phosphates are normal in amount. If an abundant precipitate gives the fluid the appearance of cream, they are greatly increased, and if a slight turbidity follows, or if the fluid remains transparent, they are decreased.

Estimation of Total Phosphoric Acid.—This is the best method of estimating the acidity of the urine (*cf.* Total Acidity, p. 47). The following method is based upon the fact that, when a solution of a phosphate acidulated with acetic acid is treated with a solution of uranium nitrate or acetate, a precipitate of uranium phosphate occurs, and when a soluble salt of uranium is added to a solution of potassium ferrocyanid, a reddish-brown precipitate is formed. The solutions required are:

1. A *standard solution of uranium nitrate or acetate*, consisting of 35.5 gm. of pure uranic nitrate or acetate in 1000 c.c. of distilled water. One c.c. corresponds to 5 mgm. of phosphoric acid (phosphoric anhydrid,

P_2O_5).* As the salts of uranium are apt to be contaminated with uranium oxid, the following method (Tyson) is recommended in preparing the standard uranium solution:

Dissolve 20.3 gm. of yellow uranic oxid in strong acetic acid previously diluted to nearly a liter. To determine the strength of the solution place 50 c.c. of the standard solution of sodium phosphate in a beaker with 5 c.c. of the solution of sodium acetate and heat on a water-bath to 90° or 100° C. The uranium solution is then allowed to run from a buret into the warm mixture until precipitation ceases.

Then a drop of the mixture is carried on a glass rod into contact with a drop of the potassium-ferrocyanid solution or a porcelain dish, and if the reddish brown uranium ferrocyanid does not appear, cautiously continue the addition of the uranium solution until the color responds to the test. The quantity used is then read off, being that which is sufficient to decompose sodium phosphate corresponding to 0.1 gm. of P_2O_5. From this is calculated the amount of distilled water to be added to make 1 c.c. of the solution correspond to 0.005 gm. of phosphoric acid.

2. *Sodium-acetate Solution.*—One hundred gm. of sodium acetate are dissolved in 900 c.c. of distilled water, and to this 100 c.c. of acetic acid are added.

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* Standard solutions for quantitative analysis may be bought already prepared, and the rather high prices of these will often appear insignificant when the time required in making such solutions at one's office is considered. The standard solutions should preferably be made by a competent pharmacist or analytic chemist, as they require testing by titration methods which are often tedious.

3. A *saturated solution of potassium ferrocyanid* to be used as an indicator.

Method.—To 50 c.c. of the urine in a glass beaker add 5 c.c. of sodium-acetate solution, and warm the mixture over a water-bath to 80° C. Drop the standard solution of uranium from a buret into the hot urine slowly, as long as the precipitate forms, or until a drop of the mixture, removed by means of a glass rod and placed on a portion of the plate, gives a distinct brown color with a drop of the indicator. This point indicates the end-reaction; the number of cubic centimeters used is read off and, multiplied by 0.005, gives the amount of phosphoric acid in 50 c.c. of urine, from which the quantity in twenty-four hours is calculated. The end-reaction, shown by the brown color on the porcelain dish, takes place when the uranium solution has precipitated all the phosphoric acid and the mixture in the beaker contains pure uranium.

Cochineal tincture is also used instead of potassium ferrocyanid as an indicator. A few drops of it are added to the urine before heating, and the standard uranium solution is added until a faint but distinct and permanent green color appears—that is, until all the phosphoric acid has been precipitated and there is a slight excess of uranium.

Phosphoric Acid with Earthy Phosphates.—To determine phosphoric acid which is in combination with lime and magnesia, 200 c.c. of urine are treated with ammonia, the precipitate is collected after twelve hours on a filter, and washed with ammonia-water (1 : 3). The filter is broken at its point, the precipitate washed into a beaker, and dissolved while warm with as little acetic acid as possible. Add 5 c.c. of sodium-acetate solution, dilute to 50 c.c., and treat as in the preceding method. The difference between the total phosphoric acid and that combined with the earths represents the quantity combined with the alkalis.

Purdy's Centrifugal Method.—Fill the percentage tube to the 10-c.c. mark with the urine and add magnesium fluid (see p. 201) up to the 15-c.c. mark. The tubes are closed, inverted several times until the urine and reagent are well mixed, placed in the centrifuge, and made to revolve at the rate of 1000 revolutions a minute for three successive periods of five minutes each. The volume percentage in normal urine is about 8 per cent. Ogden has found that each $\frac{1}{10}$ of a cubic centimeter of precipitate calculated as phosphoric acid is equivalent to 0.0225 per cent. by weight. This method is a rapid clinical way of getting the percentage of total phosphoric acid.

QUESTIONS ON CHAPTER XV.

What two forms of phosphates occur in the urine?

In what condition is the amount of phosphoric acid increased?

What is phosphaturia?

What is phosphatic diabetes?

When is phosphoric acid diminished in the urine?

How do you detect and approximately estimate earthy phosphates? Alkaline phosphates? Total phosphoric acid?

What is the most rapid clinical method for the latter?

CHAPTER XVI.

SULPHATES, CARBONATES AND LESS IMPORTANT INORGANIC CONSTITUENTS.

SULPHATES.

Two kinds of sulphates are present in the urine: (1) The ordinary alkaline sulphates of sodium and potassium ("preformed sulphuric acid"). In these the sodium salt predominates. (2) The ethereal sulphates ("conjugate sulphuric acid"), which have been described on page 156. The amount of sulphates excreted by healthy adults varies from 1.5 to 5 gm. daily. Sulphates are very soluble, and never form deposits in the urine. They are derived partly from the food and partly from the decomposition of proteids in the tissues. The albuminous food-stuffs contain sulphur, which becomes oxidized to sulphuric acid, the latter in turn combining with sodium and potassium to form sulphates of these bases. A small portion pairs off to form ethereal sulphates (one-tenth of the total sulphuric acid).

Clinical Significance.—The amount of sulphates in the urine depends normally upon the amount of proteid food. It is increased after taking sulphuric acid or sulphates; after active exercise; and after the inhalation of oxygen. It is increased in acute fever, in meningitis, and in rheumatism. As a rule, the amount of sulphates is parallel to that of urea.

Sulphates are diminished in most chronic diseases when metabolism and appetite are diminished, also after carbolic-acid poisoning or after the use of large doses of salol, etc. In such cases the ethereal sulphates are increased.

Detection.—For ordinary purposes the following test is sufficient: To a test-tube one-half full of filtered urine add one or two inches of barium solution (barium chlorid, 4 parts; concentrated hydrochloric acid, 1 part; distilled water, 16 parts). A white precipitate occurs which normally fills one-half the concavity of the test-tube. A larger amount indicates an increase, a smaller amount, a diminution.

Quantitative Determination.—The total sulphuric acid may be determined by either the gravimetric or the volumetric method.

The **gravimetric method,** according to Salkowski, consists in weighing the precipitate of barium sulphate, obtained by adding barium chlorid to a known volume of urine. One hundred parts of barium sulphate correspond to 34.33 parts of sulphuric acid (SO_3). One hundred c.c. of urine are acidified in a beaker with 5 c.c. of hydrochloric acid. Barium chlorid is added until no more precipitation occurs. The precipitate is collected on a small filter the weight of whose ash is known, and washed with hot distilled water until no more barium chlorid is found in the filtrate—*i. e.*, until the filtrate remains clear after the addition of a few drops of sulphuric acid. The precipitate is washed with hot alcohol and then with ether. The filter is removed and burned with its contents in a platinum crucible. It is cooled over sulphuric acid in a drying-oven; weighed, and the weights of the crucible and filter-ash are deducted.* The remainder is the weight of the barium sulphate formed, from which the sulphuric acid is calculated as follows: One hundred parts of barium sulphate correspond to 34.33 parts of SO_3.

Volumetric Method.—The following solutions are used: (1) A standard solution of barium chlorid made by dissolving 30.54 gm. of pure crystallized barium chlorid in water and diluting to exactly one liter. One c.c. corresponds to 0.01 gm. of SO_3. (2) A solution of potassium sulphate containing 21.775 gm. of the salt in one liter of water.

One hundred c.c. of urine are rendered acid by 5 c.c. of hydrochloric acid and heated to boiling in a flask. The combined sulphates are thus converted into ordinary sulphates. The mixture is next titrated with the barium solution, as long as any precipitate occurs, being heated before each addition of the barium solution. After adding from 5 to 8 c.c. of the solution, filter a small portion of the mixture, and to the filtrate add a few drops of the standard solution. If a precipitate occurs, return the whole to the flask, add more barium solution, and test as before, until no more precipitate is formed on the addition of barium chlorid. An excess of the latter should be avoided.

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* To correct for a slight error due to the formation of a small amount of barium sulphid a few drops of pure sulphuric acid are added after the platinum crucible has cooled, thus converting the sulphid into sulphate. Heat again to redness to drive off the excess of sulphuric acid.

If only a trace of excess is present, a drop of the clear fluid from the flask gives a cloudiness with a drop of potassium-sulphate solution placed on a glass plate over a black background. If more than a cloudiness appears, too much barium chlorid has been added, and the test must be repeated. The total sulphuric acid is calculated from the amount of barium chlorid used, 1 c.c. of the latter corresponding to 0.01 gm. of SO_3.

CARBONATES.

Minute quantities of carbonates and bicarbonates of sodium, ammonium, calcium, and magnesium are found in fresh urine of alkaline reaction. Ammonium carbonate may occur in large amounts, owing to alkaline decomposition. The carbonates in urine are derived from the food, especially from vegetable acids, such as lactic, tartaric, malic, succinic, etc.

They are, therefore, most abundant in the urine of herbivora. An excess of carbonates renders the urine turbid when passed or on standing, and, as a rule, the sediment is mixed with phosphates.

Detection.—On the addition of an acid the presence of carbonates is detected by the evolution of gas-bubbles, and this gas, when passed into baryta water, renders the latter turbid. The determination of the amount of carbonic acid will be found described in the larger text-books.

INORGANIC CONSTITUENTS OF MINOR IMPORTANCE.

Gases in the Urine.—One liter of human urine normally yields about 100 to 200 c.c. of gases, which consist of from 83 to 95 volumes of CO_2, 0.5 volume of oxygen, and from 6 to 16 volumes of nitrogen. These gases exist in solution and are separated by means of a vacuum-pump. They have no clinical significance.

Iron.—Traces of iron are found in the residue of urine after evaporation. The amount in a healthy urine varies between 0.003 and 0.0011 gm. in a liter. The exact combination in which iron occurs is still unknown. The presence of iron is detected from the ash of the evaporated residue, which is dissolved in a little hydrochloric acid, and the solution divided into two parts: the first part is boiled with a drop of nitric acid and treated with some potassium sulphocyanid solution, which produces a blood-red color in the presence of ferric oxid. The other half of the solution is boiled with nitric acid and diluted. On addition of potassium ferrocyanid a precipitate of Prussian blue is formed after standing a while.

Hydrogen Peroxid.—Shönbein found this substance in the urine in very small amounts, but so far as is known it has no significance. Dilute indigo solution is bleached by hydrogen peroxid in the presence of a solution of iron sulphate. The urine must be perfectly fresh.

Fluorin.—Hydrofluoric acid was discovered in urine by Berzelius (London, 1812), but occurs in urine only in faint traces. Berzelius found enough, however, in a considerable volume of urine to etch lines on a glass plate.

Thiosulphuric acid does not normally occur in human urine (Salkowski; Presch), but was found in a case of typhoid fever by Strümpell. It is present in the normal urine of cats and dogs. Its isolation and detection will be found described in Neubauer and Vogel, 1898, page 20.

Hydrogen sulphid (sulphureted hydrogen) is rarely present in freshly passed urine. It is not found in diseases accompanied by putrefaction, after the ingestion of sulphids, or after sulphur baths. It may pass into the urine through a rectal fistula. The chief importance of this gas lies, however, in the fact that it is formed during decomposition of purulent urine (pyelitis, cystitis). Hydrogen-sulphid-putrefaction has been ascribed (Müller, von Jaksch, etc.) to a special coccus, and according to Salkowski, the unoxidized sulphur of albumin is the source of this sulphid in albuminous urine. The presence of hydrogen sulphid may be detected by its odor (see Odor of Urine, p. 30), and by hanging in the acid urine a strip of blotting-paper moistened with lead-acetate solution and then with a drop of NaOH solution. The paper turns black, owing to a deposit of lead sulphid.

Silicic acid is present in normal urine in minute traces, and presents no clinical interest

Nitric and Nitrous Acids. According to Wulffius and Schönbein, every normal urine contains small amounts of nitrates derived from food and drinking-water. Nitric acid was found in traces in normal urines freshly passed, while nitrous acid occurs in urines after long standing, through the reduction of nitric acid. It disappears as putrefaction increases.

ACCIDENTAL INORGANIC CONSTITUENTS.

A number of inorganic substances may be present accidentally in the urine, which may otherwise be normal or may show evidences of disease.

Metals.—Mercury, arsenic, antimony, lead, silver, thallium, cadmium, and lithium have been found in urine under various circumstances. The study of their absorption, elimination, and detection belongs to toxicologic chemistry.

Halogens. Iodids and bromids appear in the urine after they have been taken internally. They are of sufficient clinical interest to merit a few words as to their detection.

When the nitric-acid test for albumin is performed, the elimination of *iodin* may be detected by the appearance of a reddish-brown zone (free iodin) at the border-line between urine and acid, the brown color gradually spreading downward into the acid.

Iodids are detected by adding chloroform to urine, then a few drops of yellow HNO_3, and shaking. The acid sets free the iodin and the chloroform becomes pink or purple.

Bromids are detected in the same manner, but more of the acid is added, and the chloroform is tinted a brownish-red.

QUESTIONS ON CHAPTER XVI.

What varieties of *sulphates* are present in the urine?

What is meant by "preformed sulphuric acid"?

What is "conjugate sulphuric acid"? How much is excreted daily in health?

Whence are sulphates in the urine derived?

What is the clinical significance of sulphates? With what other constituents do they run parallel usually?

When are sulphates increased? decreased?

Describe the ordinary test for sulphates.

How is total sulphuric acid determined?

What *carbonates* are found in fresh urine? in decomposing urine? Whence are they derived?

What is a simple test for carbonates?

How is the presence of iron detected?

In what amounts does healthy urine contain *iron?*

How is *hydrogen peroxid* in the urine detected?

CHAPTER XVII.

URINARY CONCRETIONS.

Concretions are termed sand, gravel, stones, or calculi, according to their size. They are either primary or secondary. Primary concretions are deposited from urine that has undergone no decomposition, either as a result of an excess of some normal constituents or as the result of some foreign additions to the urine. Secondary concretions are due to decomposition of the urine with the resulting precipitation of compounds of ammonia, etc., produced by such decomposition.

The classification into primary and secondary is, however, not practical and has no clinical value, as the presence of decomposition, inflammation, and suppuration in the urinary tract can always be detected from other elements in the examination of the sediment.

The most common calculi are those of—(1) Uric acid and its compounds; (2) calcium oxalate; (3) mixed phosphates. Rarer forms are made up of calcium carbonate, xanthin, cystin, and urostealith. Besides the urinary calculi, there are prostatic calculi and fibrin or blood concretions.

Uric-acid calculi are the most common. They are brown or some shade of red, usually smooth, but may be irregular. They leave only a trace of residue after ignition.

Calcium-oxalate calculi are quite common; are usually dark-brown or dark-gray, typically irregular, with more or less sharp points, and are sometimes called "mulberry calculi." They may be small and smooth ("hemp-seed calculi"). They give a considerable residue after ignition, and are soluble in acids without effervescence.

Mixed-phosphates calculi or "fusible calculi" consist of calcium phosphate and of triple phosphates of ammonium and magnesium. Phosphates may form the outer layers of other calculi of various compositions, but rarely form the nucleus of a calculus alone. Mixed-phosphates calculi are white, very brittle, melt in the blow-pipe flame, and are soluble in acids but insoluble in alkalis.

As a rule, calculi are of mixed composition if large in size, and show on section several concentric layers around a nucleus. The latter may consist of a foreign body, organic matter, such as blood-clots, or of a dense mass of calcium oxalate or uric acid.

Analysis of Calculi.—A portion of the calculus should be powdered, and when the stone is of any size, it should be sawed across, so that each layer may be examined separately. A portion of the powdered calculus is exposed on a platinum foil to dull-red heat for a considerable time. The following table from Heller is a convenient guide to the examination of calculi:

ON HEATING THE POWDER ON PLATINUM FOIL, IT

Does not burn	The powder when treated with HCl	Does not effervesce	The gently heated powder with HCl	The powder when moistened with a little KOH	Abundant ammonia. The powder dissolves in acetic acid or HCl. This solution gives a crystalline precipitate with ammonia.	Triple phosphate (mixed with unknown amount of earthy phosphates).
					No NH_3 or, at least, only traces of NH_3. Powder dissolves in acetic acid or HCl. This solution is precipitated by ammonia (amorphous).	Bone-earth (magnesium and calcium phosphate).
				Effervesces.		Calcium oxalate.
		Effervesces.				Calcium carbonate.
Does burn	With flame				Flame yellow, continuous. Odor of burnt feathers. Insoluble in alcohol or ether. Soluble in KOH with heat. Precipitated herefrom by acetic acid and generation of H_2S.	Fibrin.
					Flame, yellow, pale, continuous. Odor of resin or shellac on burning. Powder soluble in alcohol and ether.	Urostealith.
					Flame pale-blue; burns a short time. Peculiar sharp odor. The powder dissolves in ammonia, and six-sided plates separate on the spontaneous evaporation of the ammonia.	Cystin.
	Without flame				Does not give murexid test. The powder dissolves in HNO_3 without effervescence. The dried yellow residue becomes orange with alkali, beautiful red on warming.	Xanthin.
		The powder gives the murexid test	The powder when treated with KOH gives		Strong ammonia reaction.	Ammonium urate.
					No noticeable ammonia reaction.	Uric acid.

QUESTIONS ON CHAPTER XVII.

What designations are applied to *concretions* according to their size?

What are primary concretions? secondary?

What are the most common varieties? Name some rarer forms.

Describe uric-acid calculi; calcium-oxalate calculi; mixed-phosphate calculi.

What do most calculi show on section?

How is a calculus prepared for analysis?

PART III.

MICROSCOPIC EXAMINATION.

CHAPTER XVIII.

GENERAL CONSIDERATIONS.

The microscopic examination of urinary sediments should form part of the routine analysis, and should supplement the chemic tests. Very often the microscopic findings give more important clues as to the clinical conditions present than does the chemic analysis.

METHODS OF OBTAINING SEDIMENTS.

By Gravity.—This consists simply in placing the urine in a suitable glass, covering with a glass plate in order to keep out dust and foreign matter, and allowing to stand, preferably in a dark cool place, for from one to twenty-four hours. Usually about twelve hours' standing gives a satisfactory sediment. Conic glasses are used by some workers, while others prefer a glass with parallel sides and a concave bottom (Fig. 30). The edges of the glass should be ground flat and the cover should be made of ground glass.

The time required for the urine to settle is a serious objection to this method, and the decomposition which the urine undergoes on standing so long renders it unfit for microscopic examination. Casts may become disintegrated; chemic deposits altered and dissolved, and cells may change beyond recognition in decomposing urine. In order to prevent this, the addition of a crystal of thymol or of a small quantity of saturated solution of boric acid or a drop or two of formalin may be added to the urine. Of these, thymol is as satisfactory as any other preservative, but some workers prefer chloral, salicylic acid, chloroform, etc. I have already warned against the use of formalin, especially in excessive quantities, as it seriously interferes with the examination (compare p. 25).

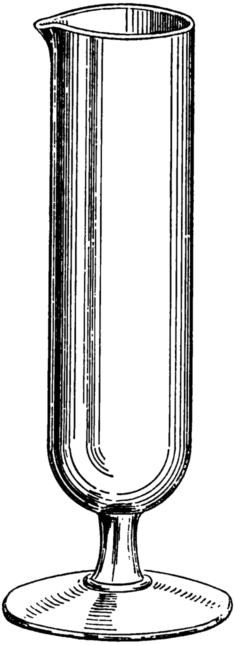
Fig. 30.—Urine or sediment glass.

Centrifugal Method. — For accurate work, the use of a centrifuge for obtaining urinary sediments is almost indispensable. In this method the urine is placed in glass tubes which are drawn out to a point, and revolved at high speed in a centrifugal apparatus, thus depositing all solids at the bottom of the tube in a few minutes. Immediate microscopic examination is then possible, and not only is there no danger of decomposition, but the sediment is more concentrated, and thus one is sure to have all the elements deposited, irrespectively of the specific gravity of the urine or the character of the sediment.

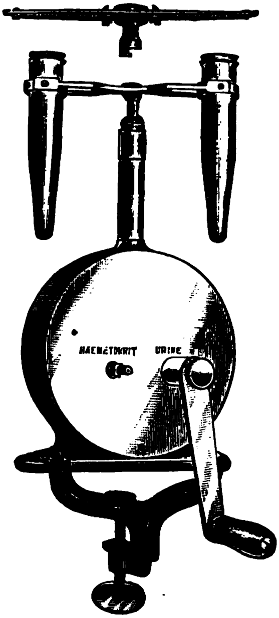

Fig. 31.—Hand centrifuge.

The simplest centrifuge is operated by hand (Fig. 31) and is satisfactory for ordinary purposes when only a few examinations are to be made daily. It gives a speed of 3000 revolutions a minute at the maximum. A water-power centrifuge which can be connected to the ordinary faucet is an excellent form of this apparatus (Fig. 32). It is very easy to operate, giving a smooth and rapid motion without much noise, and its price is moderate. The most satisfactory centrifugal machine is operated by electricity. There are numerous types, but Purdy's electric centrifuge (Fig. 33) is unquestionably the most serviceable. It can be operated either by batteries or with the street current, and is capable of all grades of speed from 500 to 10,000 revolutions a minute. With this centrifuge from three to five minutes are sufficient to precipitate all the elements of a sedi-

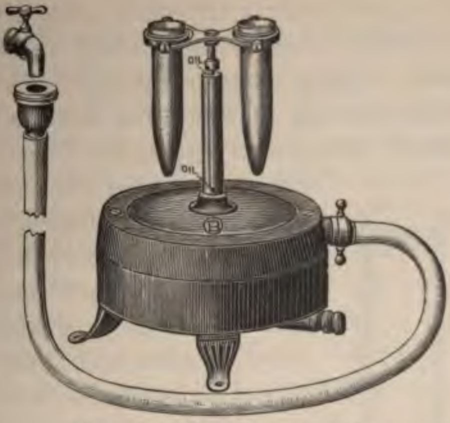

Fig. 32.—Water-motor centrifuge.

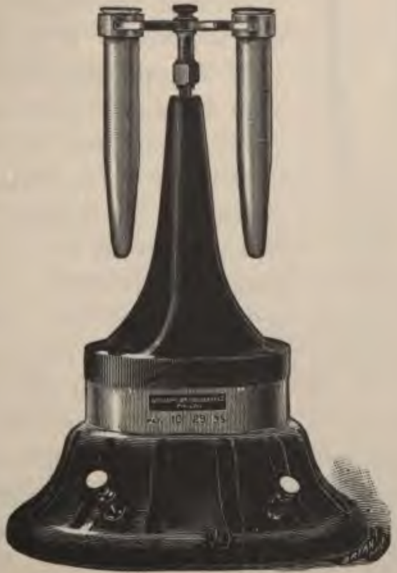

Fig. 33.—The Purdy electric centrifuge.

ment, and approximately the same time is required with the simpler centrifuges worked by hand or water power. Purdy's apparatus has arms of such lengths that the tips of the tubes describe a circle of a standard diameter of 13½ inches (Fig. 33), and can also be used for quantitative estimations of chlorids, etc., that have been described in previous chapters. All these centrifuges have aluminium shields which carry the glass tubes and are supported on elastic cushions to prevent breakage during rotation. The tubes hold about 15 c.c. each, and are made either plain or graduated. (Fig. 34.)

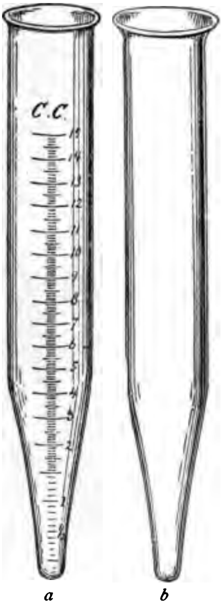

Fig. 34. — Purdy's tubes for the centrifuge: *a*, Percentage tube; *b*, sediment tube.

It is important that a worker who examines urine should become accustomed to using one centrifuge at a certain rate of speed for a certain length of time, so as to be able to compare the relative amounts of sediment and the relative proportions of the microscopic elements thereof in different specimens. A great difference as regards these points will be noted if different speeds are used for different lengths of time, or still more if the gravity method be used for some specimen and the centrifuge method for others.

METHODS OF EXAMINING THE SEDIMENT.

The sediment having been obtained in one of the ways described, a drop of it is drawn into a pipet and deposited on a slide. The pipet should consist of a simple glass tube of moderate diameter, drawn to a fairly fine point at one end. The opening at this end must not be too small, lest the tube be clogged. The upper end may have smoothed or ground edges, as the worker prefers. In drawing up the necessary sample of the sediment the pipet is to be held in the right hand, with the index closing the upper opening firmly. It is passed into the urine glass or centrifuge tube, and should almost touch the bottom thereof, then be slowly withdrawn, the pressure of the index being gently relaxed until the upper stratum of the sediment is reached. In this way the pipet will contain parts of every layer of the sediment. It must be remembered that the elements of a urinary deposit are thrown down in a certain order, the lightest coming last. Casts, mucus, and the smaller cells are among the lightest elements. The sediment is often so dense that it is better to dilute it slightly with a few drops of urine which are allowed to get into the pipet from the supernatant portion.

Two or three slides should be in readiness, perfectly clean, and free from grease and scratches. If a cover-glass is to be used, a drop of the sediment is placed on the slide and is immediately covered. The excess of urine may then be taken up with filter-paper or with a cloth. A great many workers never use cover-glasses in urinary examinations. The advantage of this is the saving of time and trouble and the possibility of going over the whole slide with the microscope instead of a limited area under the cover-glass. The disadvantages are the uncleanliness of the examination, the soiling of the lens and its mountings and of the microscope stage. If the examination be done with care, however, these features are reduced to the minimum, and the lens is not injured by the contact with urine. Needless to say that a thorough cleansing of the lens must take place if we do not want to get a part of one sediment mixed with the next specimen.

If no cover-glass is used, the sediment is deposited at first in the center of the slide and then spread in as thin a layer as possible over the entire slide, by means of the pipet held flat against the glass. If too much urine is on the slide, the mass of fluid will bulge on account of the power of cohesion, which confines it to the glass surface. In such cases it is better to drain off a drop or two from the slide, and so secure a thin layer of urine.

The next step is to place the slide on the stage of the microscope, and to examine it with the low power so as to find the places where the sediment is most promising for more minute examination. In searching for casts, for example, places where there are cloudy accumulations of sediment in masses are best selected, and their thinner parts especially are the places to look for casts. In looking for epithelia, thinner places are best selected, and the same is true in searching for crystals.

It is best to employ first the low power (Leitz objective No. 3; eye-piece IV) for all the larger elements, including casts, crystals, large epithelia and pus. The higher power (Leitz No. 7) should be used only for the minute study of casts, renal cells, and red blood-cells, etc. The exclusive use of the high power frequently makes one miss casts and other important elements which are found on a general survey with the low power.

In using the high power without a cover-glass, we must lower the lens very slowly and gently into focus, avoiding the formation of air-bubbles and the dimpling of the surface of the liquid. Unless this precaution is observed we may search for a long time in a maze of air-bubbles and foggy images before we get the clear picture through some accident. The urine should not be allowed to dry completely on the slide, nor to flood the slide in a convex layer. A thin, flat layer of urine is the secret of good work with the higher power.

In searching for casts the fine adjustment should be kept constantly changing by very slight turns of the screw. This brings different planes of a cast into view, and as casts are cylindric and often twisted, some parts are brought into focus in one position of the screw while others are not seen until the focus is changed. The search for casts is also facilitated by the use of the flat mirror; the reduction of the diaphragm aperture to the minimum, and the elimination of the Abbé condenser. In this way the faintest hyaline casts become visible.

As regards the microscope, no description is here needed, as the student is supposed to be familiar with its features. For urinary work a moderate-sized microscope of medium price is sufficient, and the objectives most useful are the Leitz's No. 3 or Zeiss' objective AA for low power, while Leitz's No. 7 or Zeiss' objective D is sufficient for the higher magnifications. An oil-immersion objective of $\frac{1}{12}$-inch diameter is not absolutely essential, but is useful in bacteriologic work in connection with uranalysis.

The microscopes made by Bausch and Lomb and by Spencer are excellent for urinary work, and may be had at lower prices than the corresponding imported instruments.

In microchemic reactions, as in testing pus-cells with iodin or acetic acid, cover-glasses must be used, a drop of the reagent being dropped close to one edge of the cover-glass.

PRESERVATION AND MOUNTING OF URINARY SEDIMENTS.

In order to preserve a sediment, we must prevent decomposition, the growth of bacteria, and other changes. This is done by allowing the sediment to settle thoroughly and by washing it in such media as will remove the soluble urinary constituents.

EXTRANEOUS MATERIALS IN THE SEDIMENT.*

It is important to know and to recognize various extraneous matters occurring in the sediment, as they often lead to errors. The admixture of these matters is derived from exposure to the air, from unclean bottles, from the feces and the external genitals, as well as the clothing of the patient.

The *fibers of textile fabrics,*—of cotton, linen, silk, and wool,—are often found in the urine. Cotton fibers are coarse, wavy, or twisted, with edges more compact in the center; the center is wrinkled and shows irregular striations. They are highly refractive. Linen fibers are less refractive and are composed of finer fibrillæ. Irregular transverse breaks

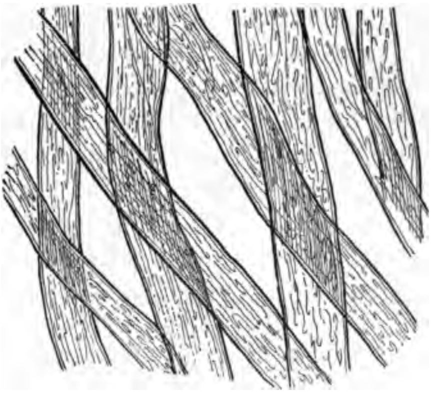

Fig. 35.—Cotton fibers.

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* I am indebted for most of the following data to Heitzmann's hand-book, which contains a detailed description of the foreign materials found in urine.

appear at different parts of linen fibers, and the outer fibrillæ are often broken off and branch irregularly from the main fiber. Silk fibers are smooth, shining, homogeneous, with jagged ends. Wool fibers are coarse and have serrated outlines, like the scales on some amphibia. They are finely striated.

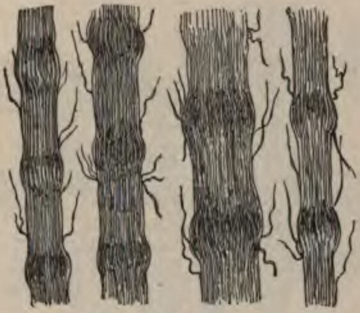


Fig. 36.—Linen fibers.

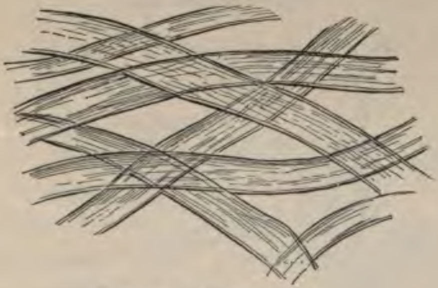


Fig. 37.—Fibers of silk.

Hairs are often found in urine, and are distinguished by their pigment, their central medullary canal, and their regular, straight outline. Particles of *feathers* show a characteristic formation, beginning with a fine quill from which branch the barbules composed of different-sized links, gradually tapering toward the end. The *scales of insect-wings* appear as delicate, transparent plates with little stems.

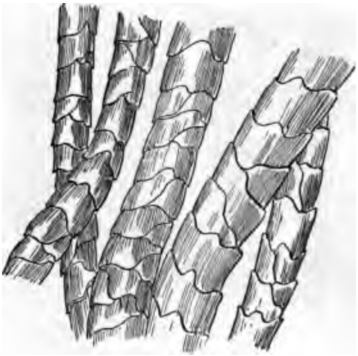


Fig. 38.—Wool fibers.

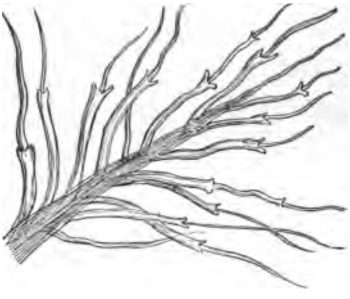


Fig. 39.—Feather.

Starch-globules are seen in the urine, owing to the use of starch powders for dusting purposes. They are oval or round, highly refractive, with a central hilum and concentric striations. Lycopodium, also used for dusting, consists of round shells studded with peculiar thorny projections. *Cellulose* appears usually in the form of a framework of cells with straight lines bounding the individual cells, which are angular or rectangular and contain large oblong nuclei. *Cork* appears in single yellowish or reddish-brown particles of irregular size, which are highly refractive, and often grouped in masses.

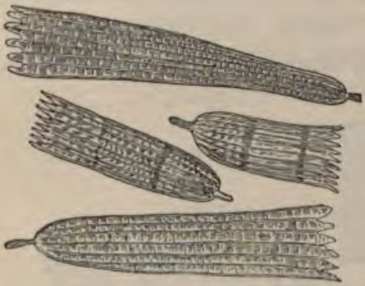


Fig. 40.—Scales from moth-wings.

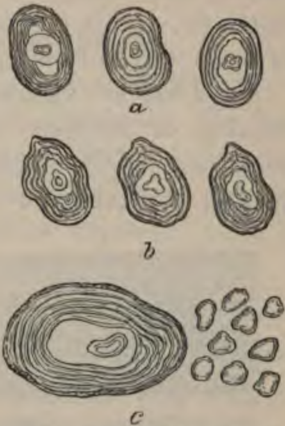


Fig. 41.—Globules of starch: *a*, Rice-starch; *b*, corn-starch; *c*, wheat-starch.

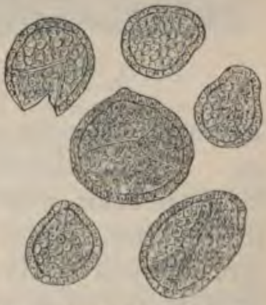


Fig. 42.—Globules of lycopodium.

Oil-globules are yellowish, highly refractive, while *air-bubbles* have sharply defined double contour and a bluish-black refraction. *Flaws* *in the glass*, scratches in the cover-glass, etc., are faint blue in refraction, and often resemble the wings of a butterfly. Rust particles may resemble hematoidin crystals, but are more irregular.

Fecal matter varies greatly in appearance. It consists of different forms of vegetable matter, such as spiral fibers from the air-vessels of plants; vegetable fibers, hairs of plants, cellulose, starch-globules, fat-globules, and crystals, spores, etc. Partly digested muscle-fibers, yellowish or brown in color, with their striations, also appear in fecal matter. There may also be connective-tissue threads, mucus threads, epithelia, pus-cells, and crystals of triple phosphate. The epithelia are usually of a flat variety, but columnar epithelia are sometimes found. Various bacteria, fungi, yeasts, etc., from the feces will also be seen. The impor-

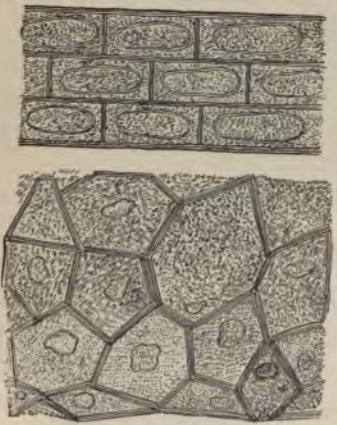


Fig. 43.—Cellulose.

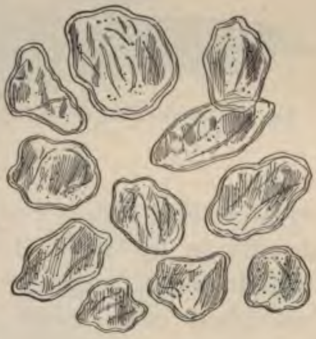


Fig. 44.—Cork.

tance of recognizing fecal material lies in the possibility of a fistula between the rectum and the urinary tract.

CLASSIFICATION OF SEDIMENTS.

The simplest classification of urinary sediments is into the unorganized and the organized. The following table from Tyson presents this classification in the most convenient form:

TABLE OF SEDIMENTS.—(*Tyson.*)

Unorganized.

- I. Urid acid (crystalline).
- II. Uric-acid compounds:
  - (*a*) Acid sodium urate (amorphous, occasionally crystalline).
  - (*b*) Acid potassium urate (amorphous).
  - (*c*) Acid calcium urate (amorphous).
  - (*d*) Acid ammonium urate (crystalline).
- III. Calcium oxalate (crystalline).
- IV. Earthy phosphates:
  - (*a*) Ammoniomagnesium phosphate (crystalline).
  - (*b*) Calcium phosphate (amorphous and crystalline).
- V. Calcium carbonate (crystalline).
- VI. Calcium sulphate (crystalline).
- VII. Leucin and tyrosin (crystalline).
- VIII. Cystin (crystalline).

Organized.

- I. Mucus and pus.
- II. Epithelium.
- III. Blood.
- IV. Casts.
- V. Spermatozoa.
- VI. Fungi and infusoria.
- VII. Elements of tumors.
- VIII. Entozoa.

Another classification divides sediments into those occurring in acid urines and those present when urine becomes alkaline. Uric acid, urates, calcium oxalate, cystin, leucin, and tyrosin are usually found in acid urine; triple phosphate, calcium phosphate, ammonium urate, and calcium carbonate, in alkaline urine.

SEDIMENTS IN ACID AND ALKALINE URINES.

The gross features of urinary sediments have already been considered in Chapter III, under the heading of Transparency, and the changes occurring in urine as the result of fermentation have been spoken of under the title of Selection of a Specimen of Urine, page 22. It is very important that the student should understand the chemistry of alkaline fermentation and of the so-called acid fermentation, so as to be able to interpret the sediments occurring in normal urine.

A *normal urine, freshly passed* and of acid reaction, contains no sediment, save the faint cloud of mucus already spoken of (p. 31), and a few epithelial cells. Urine of *alkaline reaction*, which is often normally seen three or four hours after a meal, may be more or less cloudy when passed, and may rapidly deposit flocculi of earthy phosphates, composed of amorphous granules which quickly disappear on the addition of a few drops of acetic acid.

Acid urines on standing, especially in the cold, precipitate granular amorphous matter of considerable bulk, whitish, pinkish, or reddish in color, readily soluble by heat, and consisting of urates of potassium, sodium, ammonium, calcium, and magnesium. The same urine may show, on standing still longer, crystals of uric acid of a yellow or yellowish-red color, and often the octahedral crystals of calcium oxalate. These deposits are caused by what is sometimes called *acid fermentation*. According to Scherer, this is caused by the action of the mucus of the bladder as a ferment, producing lactic and acetic acid from the coloring-matters of the urine. These acids combine with some of the bases of the neutral or alkaline urates which are in solution in normal urine, then first produce the more insoluble acid urates, which are thrown down, and later combine with the residue of the bases, leaving the crystalline uric-acid sediment.

Another explanation of the occurrence of urate deposits is that the excess of phosphoric acid in the acid sodium phosphate unites with the basic urates, rendering them acid, less soluble, and therefore precipitates them. The same process going on further, according to the length of time and the amount of acid sodium phosphate present, converts the acid urates into uric acid.

The acidity of the urine is diminished in the course of these changes, and it may become neutral or alkaline before the next stage—of alkaline fermentation—sets in.

If urine is allowed to stand still longer, or if it is kept in a warm place, especially in an open vessel, it undergoes *alkaline fermentation.* In this the urea is converted into ammonium carbonate through the action of decomposing mucus, which has a fermentative effect, or, according to some authors, through the action of a mold which multiplies within the urine and deposits with the salts in the form of a white sediment at the bottom of the vessel.

The results of the conversion of urea into ammonium carbonate are a great increase in alkalinity and a series of changes in the sediment. At the beginning of the reaction the uric-acid crystals begin to dissolve and to become fragmented, and prismatic crystals of sodium urate and dark, spheric crystals of ammonium urate adhere to the fragments of uric acid. The latter disappear altogether as the urine grows alkaline; masses of granules of amorphous calcium phosphate and triangular prisms (coffin-lid shaped) of triple phosphate (ammoniomagnesium phosphate) crowd the field, together with a number of opaque black spheres of ammonium urate, some of which show spicules (Fig. 45). In addition there are numerous spores, bacteria, infusoria, and granular matter, fragments of cells, etc.

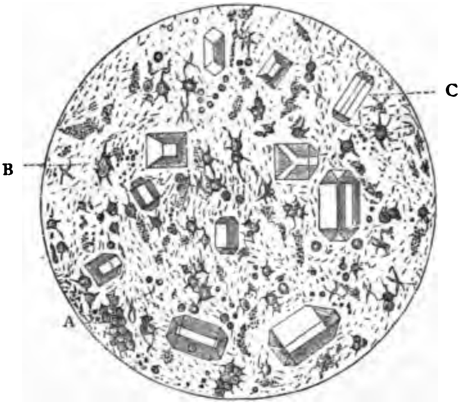
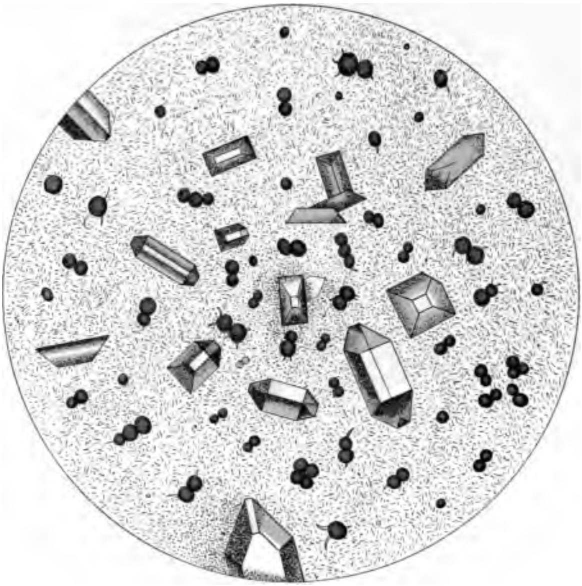


Fig. 45.—Deposits in ammoniacal urine (alkaline fermentation): A, Acid ammonium urate; B, Bacterium ureæ; C, ammoniomagnesium phosphate (Ogden).

In pathologic conditions either the sediment of acid fermentation or of the alkaline may be deposited within the body, in the pelvis of the kidney, or in

PLATE 4



Sediment of Alkaline Fermentation (*after Hofmann and Ultzmann*).

the bladder, and when urine freshly voided shows either of the sets of sediments described, we have to deal with uric-acid gravel or stone in the first instance, and with an inflammatory or suppurative condition somewhere in the urinary tract in the second.

QUESTIONS ON CHAPTER XVIII.

How are sediments obtained? Describe the gravity method; the centrifuge method.

Describe the method of preparing sediments for examination; the preservation and mounting of sediments.

What extraneous materials may be found in the sediment?

What is the importance of recognizing fecal elements?

What sediment is found in normal urine of acid reaction? Normal urine of alkaline reaction?

What is acid fermentation? What changes does it produce in urine?

What is alkaline fermentation and what sediment is found in the urine in this process?

What may be inferred when acid fermentation goes on in the urine before it is voided? If alkaline fermentation occurs so?

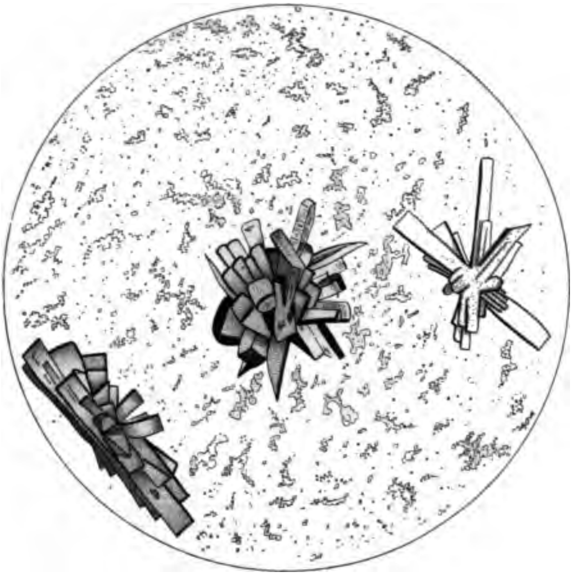
CHAPTER XIX.

UNORGANIZED SEDIMENTS.

Uric Acid.—Uric acid occurs as a heavy sediment of small bulk, sinking to the bottom, or sometimes adhering to the sides of the glass. The crystals are often large enough to be seen with the naked eye, and often form masses of yellowish-red color known as "gravel" or "sand." These crystals are frequently seen in normal urine, especially after a diet rich in meat and after exercise. They often occur at the end of the so-called acid fermentation (see p. 24); also in concentrated urine in fever, etc., and in any diseased condition in which there is an increase in the production of uric acid. It must be remembered that the occurrence of uric-acid crystals in urine is not necessarily a sign of the uric-acid diathesis, and before this diagnosis is made the diet of the patient and other conditions modifying the urine must be studied. The only safe basis for a conclusion as to the elimination of uric acid is in a quantitative chemic test.

Uric-acid crystals vary greatly in shape, but the typical forms are the rhombic or six-sided plates. Variations of this form are very often found (Fig. 46). Thus whetstone-shaped crystals, alone or in stellate groups, and crystals resembling a comb with eth on two sides, etc., are frequently met with.

PLATE 5



URIC-ACID CRYSTALS WITH AMORPHOUS URATES (*after Peyer*).

All these crystals are a more or less deeply tinted yellow, although perfectly colorless, diamond-shaped and pointed crystals often occur. In cases of uric-acid calculi uric-acid crystals often occur in masses of considerable size and irregular form. Microchemically these crystals are distinguished by adding

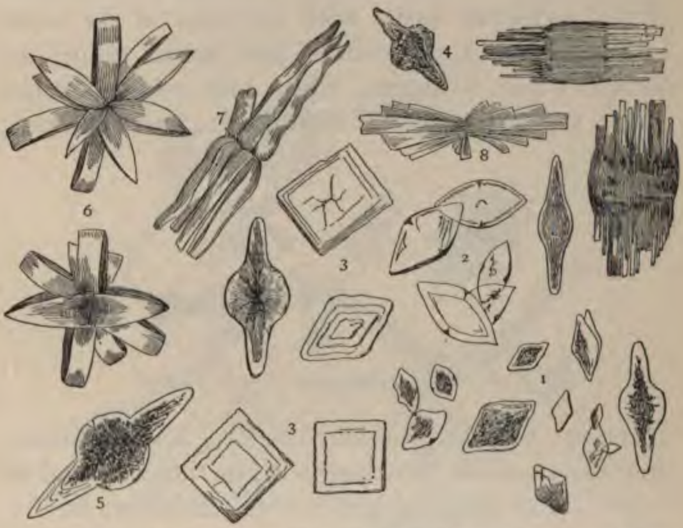


Fig. 46.—Forms of uric acid: 1, Rhombic plates; 2, whetstone forms; 3, 3, quadrate forms; 4, 4, prolonged into points; 6, 8, rosets; 7, pointed bundles; 9, barrel forms precipitated by adding hydrochloric acid to urine (Ogden).

a small amount of alkali, such as potassium-hydrate solution, while the specimen is under the microscope. The crystals will readily dissolve and will soon reappear if a drop or two of acetic acid be added. Another method is to use the murexid test. (See p. 137.)

In most instances, however, the characteristic shape and color of the crystals leave no doubt as to their character on microscopic examination.

Uric-acid Compounds.—Sodium Urate.—This is usually amorphous, and forms the greater bulk of the heavy, powdery deposit of mixed urate known as "brick-dust" or "lateritious" sediment. The color of this sediment varies with the color of the urine from which it is deposited, pale urines giving an almost white sediment, while high-colored urines give a red sediment. Sodium urate and the other urates are found in the first stages of acid fermentation, also in urine that has stood in the cold, and in fevers; after physical and mental exertion; in disorders of the stomach and intestine; on the first day of menstruation, and in various conditions where there is defective oxidation or assimilation.

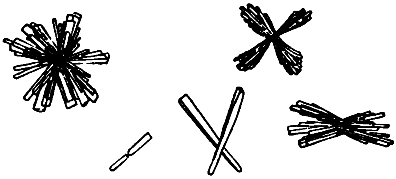
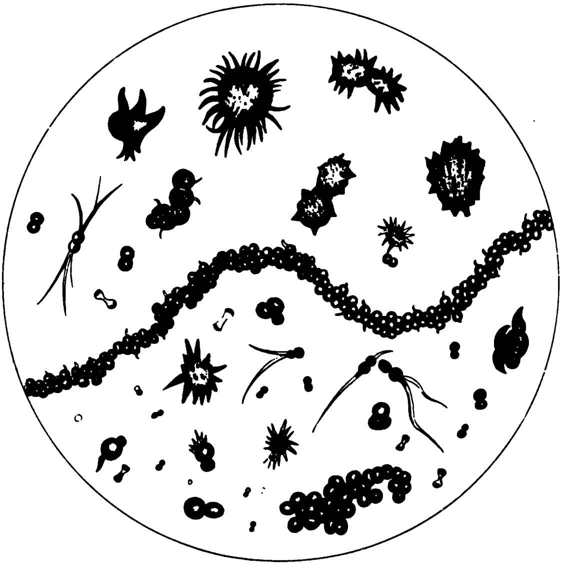


Fig. 47.—Acid sodium-urate crystals (Ogden).

Most commonly sodium urate is seen under the microscope in the form of groups of light or dark-brown, fine, amorphous granules, in moss-like masses which easily adhere to any larger elements of the sediment. Rarely, sodium urate occurs in crystals (Fig. 47), which are fan-shaped, pointed toward the center, and broader toward the periphery,

PLATE 6



AMMONIUM URATE, SHOWING SPHERULES AND THORN-APPLE-SHAPED CRYSTALS (*after Peyer*).

or arranged like sheaves of wheat. These crystals are striated in a characteristic manner.

Ammonium Urate.—This occurs in the form of yellowish-red or dark-brown spherules studded with fine sharp thorns, which have given rise to the term "thorn-apple crystals" and "hedge-hog" crystals. These thorns or spicules are sometimes curved or branched and vary in length. The salt also often crystallizes in clumps of needles arranged in sheaves. In the center of these a small spherule may be found. The crystals of ammonium urate are soluble in hot water and in acids. On addition of the latter they are transformed into uric-acid crystals. On addition of potassium hydrate the odor of ammonia is evolved. According to some observers, the spherules are really sodium urate, while the thorns are composed of uric acid (Beale, Hassall, and Thudichum). Still others claim that sodium urate undergoes a change in the urine, on standing, from the amorphous form into small dumb-bells and finally into the globules of ammonium urate, the change marking a transition of the acid sediment into an alkaline (Heitzmann).

Potassium Urate.—This is found in acid urine in the form of amorphous granules, forming a part of the mixed urate sediment. This deposit is insoluble in cold, but soluble in hot, water.

Calcium urate is rarely found, and usually in small amounts, in the amorphous deposit of urates in acid urine. It has the same solubility as potassium urate.

Method of Dealing with Amorphous Urates.—A sediment, consisting largely of amorphous urates, is difficult to examine, as many of its other elements are obscured by the abundant granules of urates. The latter may be eliminated in the following manner: The urine is allowed to settle thoroughly, is decanted, and the amount of urine decanted from the sediment is replaced by an equal amount of warm water. This dissolves the urates, and the sediment may now be allowed to settle again, or is centrifuged, and may be examined for elements other than urates. The warm water also swells and renders colorless any normal blood-cells present. Boiling water should not be used for fear of coagulating any albumin present and thus rendering the sediment unfit for examination (Ogden).

Clinical Significance of Urates.—Deposits of amorphous urates are often found in highly acid or highly concentrated urines, as, for example, in acute fevers. They are often seen also in diseases of the heart, liver, and kidneys. Ammonium urate is frequently found in the urine of newly born children. Before drawing any conclusions as to the meaning of a deposit of urates we must know the length of time the urine has stood and the temperature to which it has been subjected. Urine which deposits urates on standing in the cold may be perfectly normal, and ammonium urate is found in normal urine on alkaline fermentation. It is the only urate found in alkaline urine.

Calcium Oxalate.—This substance is often found in crystals in acid urine, together with crystals of uric acid, and also, at times, in alkaline urine, together with crystals of triple phosphate. Calcium-oxalate crystals occur in two typical forms,—the octahedral and the dumb-bell shapes,—but there are several variations of these (Fig. 48). The octahedral crystals consist of two four-sided pyramids placed base to base, and when seen from the apex of one of the pyramids, appear like squares crossed obliquely by two lines, something like the outline of a square envelop. If the long axis of the crystal is turned toward the observer, the crystal appears as a long and very sharply pointed octahedron. If several octahedra are joined, they may give the appearance of an opened umbrella. These crystals are sometimes adherent to renal casts and sometimes coalesce into larger masses.

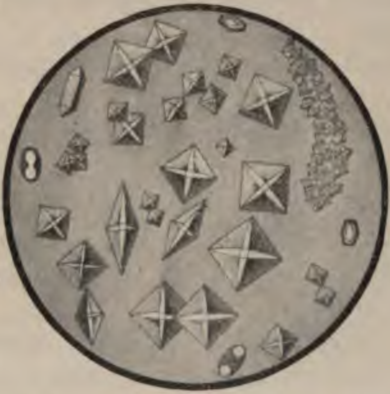


Fig. 48.—Calcium-oxalate crystals (Jakob).

The dumb-bell-shaped crystals of calcium oxalate are less frequently found, but are very characteristic. They may be crossed, forming double dumb-bells, and should not be mistaken for the yellow and brown dumb-bells of uric acid and of ammonium urate. The latter are easily soluble in alkalis, while those of calcium oxalate are soluble with difficulty. The dumb-bells of uric acid are insoluble in dilute hydrochloric acid, while those of calcium oxalate are soluble. Small circular fragments of dumb-bells of calcium oxalate are sometimes mistaken for red blood-cells. They are distinguished by the fact that they are highly refractive, colorless, and unaffected by acetic acid.

The deposit of calcium-oxalate crystals may be *primary*,—*i. e.*, formed inside the body,—and in this case the larger octahedra and dumb-bells are found. After the urine has been standing, *secondary crystals* of smaller size but similar shapes are found, often accompanied by uric acid. The large crystals may be deposited secondarily on the addition of acetic acid to the urine.

Clinical Significance.—Calcium oxalate, when present in small amounts, has no clinical significance, as it occurs in normal urines, especially after eating certain fruits and vegetables, such as apples, oranges, grapes, bananas, tomatoes, rhubarb, asparagus, spinach, and turnips, on account of the amount of oxalic acid contained in these substances. It is often increased in digestive disturbances, after an abundant diet of carbohydrates or of meat, and especially when the oxidizing power of the system is diminished. Oxalic acid is an intermediate product of metabolism between uric acid and urea, and when oxidation is diminished, oxaluria is the result. In diseases of the nervous system oxaluria is commonly observed, and some authorities claim that an excess of oxalic acid in the blood is poisonous and causes a train of nervous and other symptoms which constitutes the condition of "oxalic-acid diathesis." This is, however, a disputed point.

The occurrence of primary deposits of calcium oxalate, especially in masses of crystals and accompanied by blood or other evidences of irritation in the kidney, is usually indicative of stone in the kidney or bladder. Caution should be used in applying the term *oxaluria* indiscriminately when the deposit of oxalate is secondary—*i. e.*, occurs on standing and decomposition. A large amount of calcium oxalate occurring primarily, in a urine of high specific gravity, justifies the term oxaluria. A clinical condition known by this name has been recognized, and gives the symptoms of neurasthenia and dyspepsia, hypochondriasis, and melancholia, with headaches, general malaise, and pains in the loins. In severe forms this condition has been incorrectly called "false Bright's disease," owing to the similarity of the symptoms to those of nephritis.

Phosphates.—The earthy phosphates are the only varieties that appear in sediments of the urine. They consist of—(*a*) Triple phosphate (or ammonio-magnesium phosphate); (*b*) calcium phosphate. They occur in very feebly acid, neutral, or alkaline urine, especially after alkaline fermentation. We have already studied the gross appearance of these deposits (p. 198).

Ammoniomagnesium phosphate ($MgNH_4PO_4$), or triple phosphate, occurs in two forms—the "coffin lid" and the "feathery" or stellate crystals. The former is the most common, and consists of a triangular prism with one of the three angles wanting. These crystals are very typical and are quite large in size. At times they are shortened into squares which may be mistaken for the octahedral crystals of calcium oxalate (Fig. 49). The stellate or feathery crystals are not so common, but are found in the urine on addition of ammonia. Various stages of their evolution into triangular prisms are often seen. The shorter, square, triangular prisms are distinguished from calcium oxalate by the fact that there are larger crystals of more typical shape about them, for these atypical triple-phosphate crystals never occur alone. Besides, the phosphate crystals are dissolved by acetic acid, while those of the oxalate are insoluble in this acid.

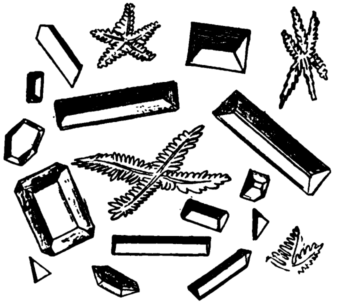


Fig. 49.—Crystals of triple phosphate (ammoniomagnesium phosphate).

Calcium phosphate is either amorphous (the normal salt, $Ca_3(PO_4)_2$) or crystalline (acid salt, $CaHPO_4$), the latter consisting partly of a deposit of magnesium phosphate. The amorphous form is often present after meals as a whitish, flaky deposit, and is precipitated by heat, but readily dissolved by acetic acid. In very feebly acid urine it is seen in small, highly refractive granules, arranged in clumps or adhering to other elements of the sediment. It is often seen with triple phosphate in neutral or alkaline urine.

The crystalline form is often seen in urine, and may be mistaken for crystals of sodium urate. Crystals of acid calcium phosphate are found in urines about to undergo alkaline fermentation, and which are still weakly acid. They are prismatic, and occur either single or in star-shaped, often in fan-like, groups. They are distinguished from sodium-urate crystals by adding acetic acid, which rapidly dissolves the phosphate crystals, while the urate dissolves more slowly and often is replaced by crystals of uric acid.

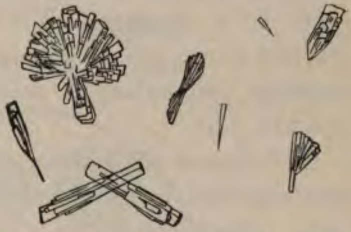


Fig. 50. — Acid calcium-phosphate crystals (Ogden).

Clinical Significance.—By *phosphaturia* is meant, properly speaking, an excess of phosphates (phosphoric acid) in the urine, and not necessarily a precipitate of phosphates. The term has been applied incorrectly to cases where the urine was normal, but less acid than usual, owing to an excess of alkalis derived from the food, and in consequence showed a precipitate of phosphates. Normal urine two or three hours after a meal, especially under a vegetable diet, very often shows a deposit of amorphous or crystalline phosphate. These deposits are not con-

By suitable illumination many of these spheres will be found marked with radiating and concentric stripes. They often are arranged in masses and chains, merging together at their edges.

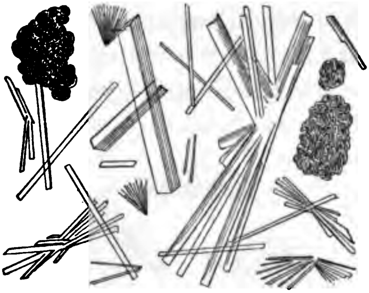


Fig. 51.—Calcium sulphate (von Jaksch).

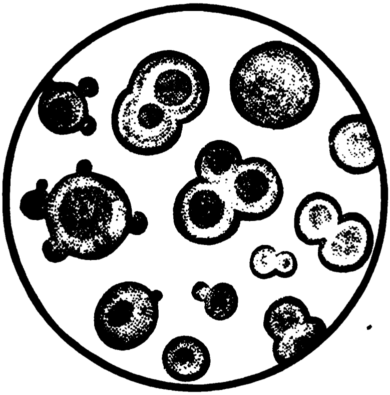


Fig. 52.—Leucin (Jakob).

The suspected urine should be evaporated slightly, and if leucin is present, the crystals will usually be deposited. The spheres are, unlike oil-globules, insoluble in ether, but are soluble in alkalis and insoluble in cold mineral acid. They are distinguished from spheres of ammonium urate by the presence of spines on the latter and by the fact that the urate is soluble on being warmed.

Tyrosin.—Tyrosin crystallizes in the form of exceedingly fine needles arranged in sheaves or in rosets radiating from the center. These crystals are colorless, but when arranged in masses, often look dark. They are tasteless, odorless, very sparingly soluble in cold water; more soluble in boiling water; almost insoluble in strong alcohol; insoluble in ether; readily soluble in acids, alkalis, and alkaline salt solutions. Tyrosin is recognized after obtaining the crystals by one of the tests described under Chemic Examination (p. 185).

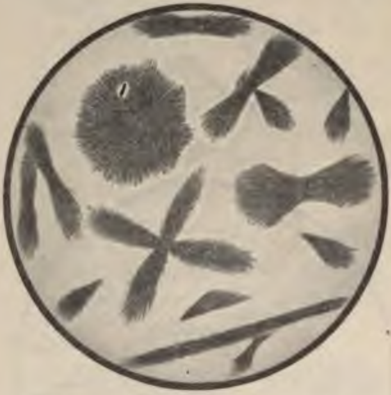


Fig. 53.—Tyrosin crystals (Jakob).

Cystin.—Cystin is a rare sediment in the urine. It occurs in crystals in the shape of hexagonal, colorless plates of moderate size and high refraction.

They are often superimposed, or may form more or less regular masses (Fig. 54). The sides of these plates are usually equal, but sometimes two sides are found shorter or longer than the others. Cystin also crystallizes in quadrilateral prisms or groups' of prisms. The crystalline sediment forms a whitish or yellowish-gray deposit, is met with in pale urine of acid reaction, and is gradually dissolved in alkaline urine, developing during decomposition the odor of sulphureted hydrogen and of ammonia.

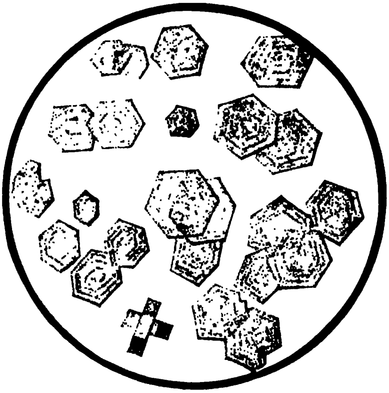


Fig. 54.—Crystals of cystin (Jakob).

Cystin sediment is soluble in ammonia, in mineral acids, and in alkaline hydrates and carbonates, except ammonium carbonate. It is insoluble in alcohol, ether, and water, and is precipitated from alkaline solutions by acetic acid. Its solutions rotate the plane of polarized light toward the left. Cystin is an amido-acid with the formula of C_3H_6-NSO_2, and contains 26 per cent. of sulphur, which gives rise to the odor of sulphureted hydrogen already spoken of. The crystals are not readily confounded with uric acid, but they may be treated with ammonia and the solution evaporated. If the crystals are uric acid, ammonium urate will form and will remain as an amorphous residue. Hydrochloric acid also readily dissolves cystin, but leaves uric acid unchanged. Acetic acid redissolves triple-phosphate crystals, but leaves cystin unaltered. The presence of cystin should be suspected in all urines in which an odor of sulphureted hydrogen is detected.

Clinical Significance.—Cystin is probably not present in normal urine. In disease the amount varies, and the daily quantity may reach as high as 1.5 gm., although ordinarily it is very much smaller. The cause of cystinuria is not definitely known. Brieger and others have found that certain products of intestinal putrefaction—the *diamins*—are eliminated in the urine and feces of persons with cystinuria. These diamins are said to arise only as the result of putrefaction due to specific germs, and cystinuria may be regarded as the result of specific intestinal infection. As yet no definite relation has been found between the formation of cystin and of the diamins, although both occur under the same conditions. Heredity seems to play some rôle in cystinuria, as many cases have occurred in several members of the same family. Both infants and adults may eliminate cystin, but it rarely occurs in old age. It may not be connected with any symptoms, although present for years; but usually there are symptoms of irritation in the urinary tract. It has been observed in some cases of liver disease and of acute articular rheumatism.

Bilirubin and Hematoidin.—**Bilirubin** may be found in amorphous or crystallized form in the sediment of urine containing bile. The crystals occur as needles in stellate clusters, often adhering to cells, or in the form of minute rhombic plates varying in color from yellow to ruby-red. They are soluble in sodium hydrate, and on the addition of nitric acid they show a green rim.

Hematoidin is a derivative of hematin, and was first found by Virchow in extravasated blood. Its crystals are identical in shape and all other respects to those of bilirubin, and probably the two are identical. These crystals are found not uncommonly in urinary sediments after extensive hemorrhage, the evacuation of an abscess, or in pyonephrosis. They have been found in nephritis of pregnant women, in acute yellow atrophy, cirrhosis of the liver, severe persistent jaundice, phosphorus-poisoning and cancer of the bladder.

Fat-globules.—Fat occurs quite frequently in the urine, but we must be careful not to confound it with that from outside sources contaminating the specimen, which, as a rule, occurs in larger, more irregular, and more yellowish globules. When enough fat is voided to be seen by the naked eye, and when little or no albumin is present, the term "*lipuria*" may be applied. When urine presents a milky appearance with a creamy layer on top on standing, the term *chyluria* is used. The latter has already been discussed on page 186. Microscopically, fat-globules and granules vary in size, and when the larger ones are found, there may also be some slender needles of margaric acid lying between the globules or even within them. Fat-globules are recognized by their dark contour and high refraction.

Aside from the cases of chyluria and lipuria (the latter has been observed in health temporarily after a fatty diet, in pregnant women, and in phosphorus-poisoning), a small number of fat-globules is seen in a great many cases of chronic inflammation in the genito-urinary tract. These globules are probably a product of protoplasmic degeneration, as they are found both free and in masses within epithelial and pus-cells. They are more numerous in the chronic cases, and often the cells may be completely changed into masses of fat-granules. These globules are found in chronic nephritis, pyelitis, cystitis, prostatitis, urethritis, and vaginitis.

They are especially interesting in fatty casts. (See p. 284.)

Cholesterin is occasionally found in urinary sediments. It crystallizes in large, colorless, transparent plates whose angles and sides are often broken, and whose acute angles are often as small as 76 degrees. Larger masses of these crystals have a pearly luster and a greasy feel. The occurrence of cholesterin and its chemic characters have already been considered (p. 187). It is readily detected in the urinary sediment by means of the microscope. If a mixture of five parts of sulphuric acid and one part of water be allowed to act upon the crystals, a bright, carmin-red color appears which changes to violet. Another method of testing under the microscope is by adding dilute sulphuric acid and then a solution of iodin. The crystals will show a play of colors beginning with violet, then bluish-green, and finally blue. (*Vide* Fig. 29.)

QUESTIONS ON CHAPTER XIX.

Name the principal forms of unorganized sediments.

How does *uric acid* occur in the urinary deposits?

What does the presence of uric-acid crystals indicate? What simple chemic tests may be used to distinguish these crystals?

Describe the appearance of deposits of sodium urate; ammonium urate; potassium urate; calcium urate.

How are urates eliminated from a urinary sediment?

What is the clinical significance of urates?

Describe the two forms of *calcium-oxalate* crystals. How are the dumb-bells distinguished from those of uric acid and of ammonium urate? From red blood-cells?

What is meant by a primary deposit of calcium oxalate?

What is the significance of calcium-oxalate crystals? What diet favors the appearance of these crystals in the urine?

In what conditions and diseases is oxalic acid increased?

When should we apply the term "oxaluria"?

What is meant by "oxalic-acid diathesis"? By "false Bright's disease"?

What *phosphates* occur in the urinary sediments? In what reactions of urine do they occur?

In what forms do triple-phosphate crystals occur? How are the square prisms distinguished from calcium oxalate?

What two forms of calcium phosphate are found in sediments? How is the crystalline form distinguished from sodium urate?

What is meant by *phosphaturia?* What does phosphaturia indicate?

When are primary sediments of phosphates found?

What *carbonate* compound is sometimes seen in sediments? How is it distinguished? What *sulphate*, and how does it occur?

Describe the appearance of deposits of *leucin;* of *tyrosin;* of *cystin.*

What odor does cystin develop during decomposition? How is this substance distinguished from uric acid? What is the clinical significance of cystin?

Describe the crystals of *bilirubin* and *hematoidin* and state their clinical significance.

What mistake is often made in connection with *fat* in the urine?

What is meant by lipuria? By chyluria? When does lipuria occur?

What does a small number of fat-globules indicate? In what conditions are they found? Describe their appearance.

What is the appearance of *cholesterin* crystals? What reaction do cholesterin crystals give with H_2SO_4 and iodin?

CHAPTER XX.

ORGANIZED SEDIMENTS.

The second group of sediments includes cells, fibers, and other formed elements of various parts of the urinary tract, some of which are normally present in the urine, while others indicate some disturbance or disease. The study of the organized sediments is the most important portion of the microscopic study of the urine, as upon the recognition of these elements very largely depend the localization of the diseases of the urinary tract and the determination of the nature and stage thereof.

BLOOD.

With the exception of the urine of women during menstruation, etc., in which the presence of blood is unimportant, the occurrence of red blood-cells in urinary sediments is always abnormal. Red cells vary in appearance according to the part of the tract from which they come, according to the freshness of the specimen, and according to the concentration of the urine, the presence or absence of decomposition, etc.

Normal blood-cells—*i. e.*, cells so unaltered that they look very much like cells in fresh blood—are very characteristic in appearance. They are biconcave discs of a yellow color, considerably smaller than the white cells, about $\frac{1}{3200}$ inch in diameter, without nuclei, granules, or other visible cell-contents. On careful focusing the relations of light and shadow at the center and periphery alternate as the objective is approached to the slide or removed from it.

The first change that blood-cells undergo in the urine is the alteration in outline known as "crenated," irregular, or "mulberry shaped." This may be found in urine with a high percentage of sodium chlorid.

Abnormal Blood-cells.—Blood-cells which have entered the urine within three or four hours begin

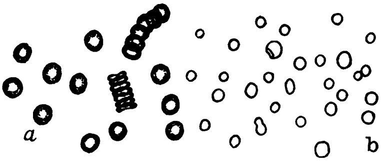


Fig. 55.—Blood-corpuscles: *a*, Normal; *b*, abnormal (Ogden).

to lose their color and swell until they are mere rings or shadows. Instead of being biconcave, they become almost spherical, very pale or almost colorless, and about two-thirds of the normal cells in diameter. Any blood-cell which has lost its yellow color is "abnormal."

Normal blood, when present in large amounts, produces, in alkaline urine, a bright-red color, and in highly acid urine, a brownish-red color. Abnormal blood, if present in sufficient amount, renders the urine brownish or smoky, and if in large amounts, almost black. Very commonly, however, the amount of blood is so small that it can be detected only microscopically. Urine containing blood always gives a reaction for albumin, even if the amount is minute.

Detection.—The chemic detection of blood by Teichmann's method has already been described on page 178. The crystals of hemin which are thus obtained are brown, rhombic plates, the proper chemic name of which is hematin iodid or chlorid. The crystals are very small, and often crossed or arranged in groups (Fig. 56). This test is useful when there is any doubt as to the presence of blood in the urine.

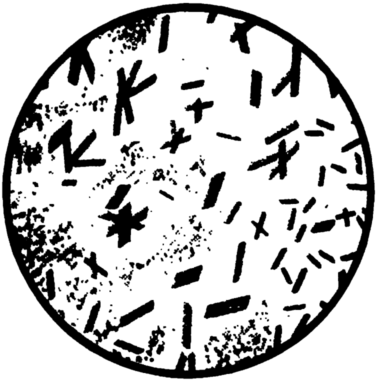


Fig. 56.—Teichmann's hemin crystals (Jakob).

To Remove Blood from a Sediment.—The blood-cells may be so abundant in the sediment that they obscure everything else, and must be destroyed before examination. This is done as follows: The urine is allowed to settle slowly, the supernatant fluid is decanted, and a large amount of lukewarm water, with a few drops of dilute acetic acid, is added to the sediment. The mixture is stirred thoroughly, breaking up all clots, and allowed to settle again. The process is repeated until the water is free from color; the sediment is allowed to settle and examined. The blood-cells are washed out and almost invisible, while casts, etc., can be seen.

Clinical Significance of Blood.—We have already considered the subject under the heading of Blood-Pigments (Chapter XII, p. 176). The distinction between hematuria, in which blood-corpuscles are present together with blood-pigments, and hemoglobinuria, in which the pigment alone appears, can be made with the microscope. The first purpose of microscopic examination in connection with blood is to locate, if possible, the source of the hemorrhage.

Blood from the Kidney.—As blood from this organ is usually in contact with urine for a considerable time before it passes out, it is generally abnormal in character and more or less dark brown or smoky. In injuries to the kidney, in acute congestion, etc., however, the blood may be normal and bright red. The reaction of the urine containing blood in the kidney is usually acid, although it may be alkaline if the amount of blood be large. A characteristic feature of blood from the kidney is that it is often accompanied by casts to which red cells adhere. This is the only positive evidence that blood comes from the kidney. Blood-clots may be found in such urines, but are usually small.

GUIDE TO THE ORIGIN OF BLOOD IN HEMATURIA.—(*After Oertel, as quoted by Brooks.*)

Origin.	Quantity.	Differential Points.	May Occur in
Kidney.	Usually comparatively small.	Clots usually absent. Associated with blood-casts, epithelial and hyaline casts, renal epithelium. Intimately mixed with urine. Many swollen (loss of hemoglobin) phantom corpuscles. Sediment slight (or abundant).	Acute and chronic nephritis. Malignant growths. Renal calculus, tuberculosis, embolism, abscess, acute febrile processes, hemophilia, and in filariasis (malaria) and distomiasis. Frequently in poisoning from turpentine, etc.
Pelvis of kidney and ureters.	Variable.	Absence of casts of any kind, or renal epithelium. Fibrinous molds of ureters may be present. Pus-cells in calculus.	Diseases of pelvis, calculus, etc.
Bladder.	Frequently large.	Blood-cells well preserved unless urine is ammoniacal; clots frequent. Heavy sediment (often scanty). Pus in cystitis. Shreds of tumor tissue in papilloma or malignant growths. If neck of bladder involved, blood appears at end of micturition.	Stone, cystitis, tumors, varicose veins of vesical neck, Distoma hematobium, etc.
Urethra.	Small.	May be expressed; first part of micturition.	Urethritis, trauma, etc.

The causes of bleeding from the kidneys are acute congestion and acute nephritis, in each of which the amount of blood varies considerably, according to the severity of the condition. In chronic nephritis a small number of red cells may be found, but during an exacerbation there may be an abundant bleeding, fresh blood-cells appearing suddenly with a dimtion in the daily quantity of urine. In chronic interstitial nephritis blood is not infrequently found as the result of disturbances in circulation caused by heart disease or by diseased arteries. In amyloid kidneys hemorrhage occurs sometimes, owing to the infiltration around the small blood-vessels.

The three great causes of blood in the urine are tuberculosis of the kidney, tumors of the kidney, and stone in the kidney. In tuberculosis the bleeding may be intermittent or continued for a long period, and is accompanied by pus in considerable amounts. The diagnosis is made by finding tubercle bacilli in the sediment. In tumors of the kidney blood appears in considerable amounts at times, usually in attacks. Here, also, there is usually pus in the urine, and the sediment contains at times a number of cells which resemble the characteristic elements of the tumor. Stones in the kidney or in the renal pelvis give rise to either constant or intermittent bleeding. The urine may contain pus and fragments of stone or masses of crystals which hint at the presence of calculus. It must be remembered that in the early stages of tuberculosis, of tumors of the kidney, and of stone there may be no bleeding, but, as a rule, the appearance of blood in these conditions occurs sufficiently early to call attention to the possibility of one of these diseases, and unless their presence can be eliminated, the occurrence of attacks of hematuria is a sufficient basis for suspecting one of these three conditions. The study of the clinical symptoms, especially of the presence of
olic, and tumor, and the study of the epithelial

elements and of pus-cells and crystals, as well as the examination for tubercle bacilli, will usually lead to a diagnosis.

Certain drugs which irritate the kidney, such as cantharides, turpentine, etc., may give rise to hematuria. Wounds, contusions, concussion of the kidney by indirect injury, and the invasion of the kidney by parasites (see p. 300) are also causes of bleeding. Other sources of hemorrhage in the kidney are cysts of that organ, purpura, and renal embolism.

Hemorrhage from the Pelvis and Ureter.—There is nothing microscopically characteristic about bleeding from the ureter, but the passage of thin, cylindric clots may help in the diagnosis. The presence of a large number of epithelial cells from the ureter may assist in localizing the trouble. The causes of these hemorrhages include acute pyelitis, stone, acute ureteritis, injuries, etc.

Bleeding from the bladder is seen in moderate amounts in acute and chronic cystitis, but the most important causes of this bleeding are the same as in the case of the kidney—*i. e.*, stone, tuberculosis, or tumor of the bladder. Blood from the bladder is usually normal or comparatively unchanged; but if the urine is highly acid or alkaline, or if there is retention and the blood remains in the bladder for a long time, the blood-cells are abnormal. Bleeding from the bladder is characteristically associated with clots—at least more so than bleeding from the upper urinary organs. As a rule, pus is present in all conditions of the bladder accompanied by bleeding, the exception of injuries, surgical operations, etc. In the diagnosis of the cause of the bleeding from the bladder the sediment must be examined for characteristic cells or fragments of a tumor, for crystalline masses or fragments of a stone; for tubercle bacilli, gonococci, or other bacteria.

PUS.

Pus-cells or leukocytes occur in the urine in the form of small, round, granular bodies about twice the size of normal red blood-cells. They contain one or more nuclei, which may or may not be seen in the specimen, but appear very clearly on the addition of acetic acid. As a rule, they can be easily recognized, but if any doubt arises as to their nature it may be dispelled by the addition of a little solution of iodin and potassium iodid. The leukocytes stain a deep mahogany-brown (glycogenic reaction), while epithelium, which may resemble them, assumes a light-yellow color. In freshly passed urine leukocytes may exhibit active ameboid changes and assume irregular outlines. In dilute and highly alkaline urine they become swollen, globular, and hydropic, and the granulation in them becomes pale or disappears. In ammoniacal urines the pus-corpuscles may burst and coalesce into a sticky mass.

The amount of granulation varies widely in pus-corpuscles, and the granules may be coarse or fine. Heitzmann claims that coarse granulations are indicative of a good constitution in the patient, while finely granular and pale pus-corpuscles indicate a poor and broken-down constitution. In some cases minute fat-globules appear in the pus-cells, and the whole cell may be replaced by them. This is never found in acute inflammations, and the more fat-globules are found, the more chronic the process is, in all probability. Pus-cells may contain rust-brown crystals of hematoidin in

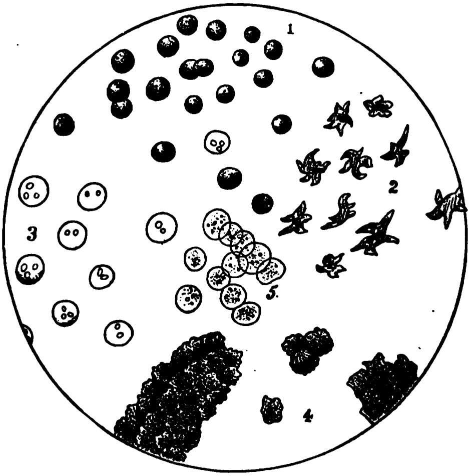


Fig. 57.—Pus-corpuscles: 1, Normal corpuscles; 2, pus-corpuscles with prolongations showing ameboid movements; 3, pus-corpuscles with nuclei rendered distinct by acetic acid; 4, pus-corpuscles altered by chronic pyelitis; 5, pus-corpuscles swollen by ammonium carbonate (after Ultzmann).

the form of needles or flakes, especially in cases in which pyuria is accompanied by hemorrhage. Dark-brown pigment-granules may be found in these cells in chronic cystitis. Very rarely pus-cells may show delicate cilia, showing their origin from the epithelia of the uterus (endometritis).

As has been intimated above, the pus-cells in the urine are practically identical with the leukocytes of the blood. They may be derived from the substance or the pelvis of the kidney, the ureters, the bladder, the urethra, or from the rupture of an abscess into some portion of the urinary tract. Pus-corpuscles in the urine are also largely derived from the connective tissue and from the epithelia of the various organs of the urinary tract. For this reason they bear at times characteristics of the epithelium whence they come—as, for example, the pigmented pus-cells of chronic cystitis.

Clinical Significance.—A few leukocytes may be seen in perfectly normal urine. When present in moderate numbers, the presence of an inflammation somewhere in the tract may at once be suspected. When they are very numerous, the diagnosis of suppuration may be made, provided the other features of the urine corroborate it. The presence of pus having been determined, the next step is to find its source, and the only way to do this is to study the other elements of the sediment, such as epithelia, casts, etc., which accompany the pus.

Pus from the kidney may be found in any inflammatory or suppurative condition of this organ. A few cells will be found in simple irritation and in non-suppurative nephritis, showing that the pus-cells are the product of an inflammation. In chronic nephritis pus-corpuscles containing fat-globules and granules are frequently observed. In suppuration of the kidney and pelvis (pyelonephritis) due to ascending infection from the bladder or to a stone, a tumor, or a tuberculous process, the presence of pus is a prominent feature. Pus from the kidney or pelvis is also seen in urine from abscess of the kidney, suppuration of the pelvis (pyelitis), and pyonephrosis. In cases of abscess of the kidney there may be no pus before the abscess ruptures into the pelvis or into a pocket communicating with this part, when there will be a sudden appearance of pus. The same will be observed when there is a sudden removal of an obstruction in the pelvis or ureter.

Pus from the bladder is seen in acute and chronic inflammation and in stone, tumor, or tuberculosis of the bladder. **Pus from the prostate** may be present in prostatitis, prostatic abscess, and **pus from the urethra** in urethritis, especially of gonorrheal origin. It is important to distinguish, in the urine of women, **pus which comes from the uterus or vagina,** and if there is any doubt, the urine should be obtained by catheter or should be voided after a thorough vaginal douche.

The mucus-corpuscle which occurs in the urine is a small, granular, rounded cell, somewhat larger than the red blood-cell, containing one or more nuclei. The size varies, however, within considerable limits, and the single nucleus is more common, while in the pus-corpuscles the multiple nucleus is characteristic. The distinction between a mucus-corpuscle and a pus-cell is functional rather than morphologic. A pus-corpuscle is a product of a pathologic process, while a mucus-corpuscle is nothing more than a young epithelial cell which reaches the surface of a healthy mucous membrane before it has attained its full development as an epithelial cell. Anatomically, the mucus-corpuscle resembles the pus-corpuscle so closely that it is practically identical, the only difference being that the mucus-corpuscle generally contains one nucleus or none that is visible, and is always pale and finely granular. In the same way the leukocyte is anatomically identical with the pus-corpuscle, while functionally the two are distinct.

CONNECTIVE-TISSUE SHREDS.

The occurrence of connective-tissue shreds in urinary sediments was first pointed out by Carl Heitzmann. They are found in the form of sinuous, highly refractive fibers, single, or more often in irregular bundles, and finely fibrillated or granular. Their thickness and length vary within wide limits. They are distinguished from mucus-threads by their high refraction, their fibrillated appearance, and wavy outlines. Linen fibers are coarser, not so wavy, and of higher refraction than connective-tissue shreds.

Connective-tissue fibers in the sediment indicate a new growth or an ulcerative, suppurative, and to a lesser degree an intense inflammatory lesion of the genito-urinary tract.

In chronic interstitial nephritis and in chronic diffuse nephritis connective-tissue shreds may be present in the urine along with other microscopic features. According to Heitzmann, their presence is of great diagnostic value in these cases. In tuberculosis of the kidney, in tumors, or in stone of the kidney these shreds may also be present and indicate an intense destructive or inflammatory condition. Tumors of the bladder, especially cancer and papilloma, may also be accompanied by the appearance of these shreds, in conjunction with more typical tumor elements. Connective-tissue shreds may also occur in company with pus in abscesses from various portions of the genito-urinary tract and in hypertrophied prostate.

Whenever these shreds appear in the urine, they indicate a disintegration of connective tissue, consequently they are, as a rule, signs of deep-seated and serious lesions in the tract.

EPITHELIUM.

Epithelial cells from various parts of the urinary tract occur in both normal and pathologic urines. In normal urine the epithelia are few or moderate in number, and represent the shedding of the surface layers from the ordinary wear and tear of the parts. In pathologic conditions not only is the number increased, but the cells are altered and the elements characteristic of the deeper layers appear together with those from the superficial strata.

It may be said that every part of the urinary tract has theoretically its characteristic epithelium. *In practice, however, it is not always possible to say of a given cell in a urinary sediment just where it came from.* It is possible, however, to find enough cells bearing the characteristics of epithelia from a given part to form a judgment as to the portion of the tract which was the source of the desquamation. The farther away we get from the bladder, the more difficult is it to distinguish the epithelia of one part of the tract from those of another. One thing must be borne in mind, to begin with, in studying the epithelia of the urine; namely, that the epithelium, as found in urinary sediments, usually has entirely different outlines from that found histologically in the portion of the tract whence it came. This is due to the changes which apparently take place in the process of maceration in the urine. The whole basis of distinguishing certain epithelia from the kidney,

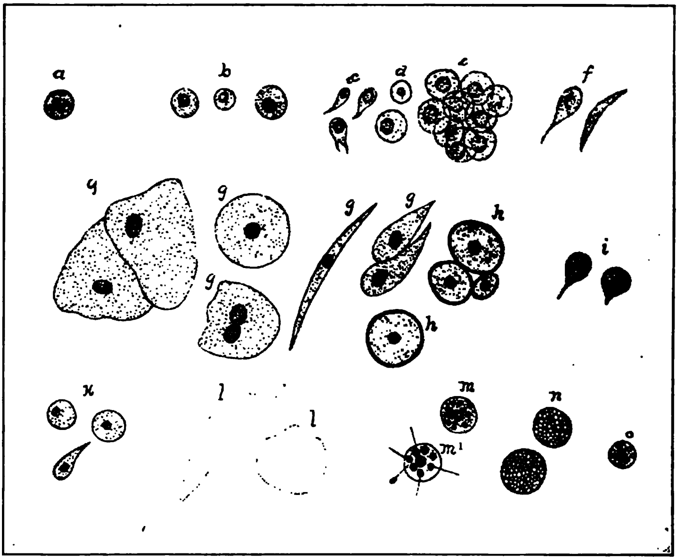


Fig. 58.—Epithelium from various parts of the urinary tract: *a*, Leukocyte (for comparison); *b*, renal cells; *c*, superficial pelvic cells; *d*, deep pelvic cells; *e*, cells from calices; *f*, cells from ureter; *g*, *g*, *g*, *g*, *g*, squamous epithelium from the bladder; *h*, *h*, neck-of-bladder cells; *i*, epithelium from prostatic urethra; *k*, urethral cells; *l*, *l*, scaly epithelium; *m*, *m'*, cells from seminal passages; *n*, compound granule cells; *o*, fatty renal cell (Ogden).

for example, from others derived from other parts, is the size of the cells as compared to a standard. As a rule, the standard cell of a urinary sediment is the leukocyte or pus-corpuscle, because it varies but little (Fig. 58).

Before studying the different epithelia in the urine we may briefly refer to the different types of these cells occurring in the body. They are of three varieties: The flat or squamous; the cuboidal; and the columnar or cylindric. The latter may be ciliated, having one or more hair-like processes on one surface. All epithelia have one or more nuclei, and their cell-bodies are finely or coarsely granulated. When epithelia are stratified, the upper layers are usually flat, the middle layers cuboidal, and the inner layers columnar.

Stratified epithelium is found in the pelves of the kidneys, in the ureters, bladder, urethra, vagina, and cervix of the uterus. A simple epithelial lining is found in the tubules of the kidney, in the prostate, the ejaculatory ducts, and the mucosa of the body of the uterus.

The size of epithelia from different organs and parts of the genito-urinary tract varies considerably. The largest epithelia are found in the vagina; the next in size in the bladder; then, in order, the epithelia of the cervix, the urethra, renal pelves, ureters, and prostate, while the smallest are found in the tubules of the kidney. As has been hinted before, there are transitional sizes and shapes which cannot be regarded in diagnosis. It is the average size and the average shape that count.

Epithelia from the Bladder.—The upper layers are flat, the middle layers cuboidal, the deepest layers columnar. A small number of the flat epithelia appears in every normal urine and has no significance. If they appear accompanied by pus and with cuboidal epithelia, they show disease in the bladder. The flat epithelia are found free or in pavement clusters of irregular size and shape. They are smaller than the cells from the upper layers of the vagina, but near the neck of the bladder they become quite large and may be confounded with vaginal epithelia. They do not contain bacteria, however, as the latter frequently do. Cuboidal epithelia from the bladder, when present in moderate or large numbers with the flat epithelia from the upper layers, indicate an acute cystitis. Cuboidal epithelia alone, without the upper layer, indicate a chronic cystitis, and the presence of columnar epithelia from the deepest layer of the bladder indicates deep ulceration, tumors, or an intense inflammation. Cuboidal and columnar epithelia may contain fat-granules, which indicate a chronic process. In the epithelia from the middle layers the formation of so-called endogenous pus-corpuscles may be observed—that is, pus-corpuscles are formed within the epithelia, especially in cases of hypertrophied prostate, of uterine tumors pressing on the bladder, or any other condition which keeps up irritation or pressure from the outside.

Epithelia from the Pelvis of the Kidney.—The epithelium in this part is very irregular in shape. The characteristic form is the caudate, pear-shaped, or lenticular, but round and cuboidal shapes, smaller than bladder epithelia, also occur. The pelvic cells are smaller than those from the bladder and larger than those from the ureter. The caudate cells come from the superficial layer of the pelvis, and often have curved or bifurcated tails. They are of the same size or a little larger than leukocytes, and have distinct nuclei and well-marked granules. Their presence indicates irritation or inflammation in the renal pelvis, and they occur in large numbers, with pus, in pyelonephritis. The round-cells, which are less frequently found, closely resemble the renal cells, but are often arranged in clumps and are always accompanied by pus. They are derived from the deep layers of the pelvis and indicate chronic pyelitis.

Epithelia from the Ureters.—These are especially seen in specimens obtained by the ureteral catheter, but occur in urine usually mixed with pelvic epithelium. Two forms of epithelial cells from the ureter are seen: (1) A small caudate cell, somewhat larger and denser than the cells from the upper layer of the pelvis, with a larger and more prominent nucleus and a larger tail; (2) a small spindle-cell, very narrow, with a small nucleus. These cells are distinguished from columnar cells in the bladder by the fact that they are much smaller. The ureter is rarely affected alone, except by irritation from stone, etc., and the presence of cells from the ureter is almost always accompanied by the signs of pyelitis or cystitis.

Renal Epithelium.—The characteristic epithelial cell from the tubules of the kidney is small, round, more or less granular, with a single nucleus. These epithelia are the most important of all the cells found in the urine, and at the same time are the most difficult to recognize and the most frequently overlooked. They are never seen in normal urine, and their presence, even without casts but with a few pus-corpuscles, is sufficient to make a diagnosis of nephritis (Heitzmann). Two forms are distinguished—the cuboidal, from the convoluted tubules, and the columnar, from the straight collecting tubules. Renal epithelia are much smaller than those of the pelvis of the kidney or of the ureter in the same person.

The correct method of looking for renal epithelia is so clearly set forth by Heitzmann that I quote it literally:

"In every case examined, the first step is to look for pus-corpuscles, which are known to be small in some people and are usually the smallest granular corpuscle seen. As soon as these are decided upon, the next step is to determine whether bodies distinctly larger than these are present. If such bodies, one-third larger than pus-corpuscles, are found in at least moderate numbers, we can be certain that they are epithelia from the convoluted narrow tubules of the kidney. The presence or absence of nuclei has no significance whatever, although such a nucleus is usually found in the kidney epithelia, but may be invisible in the pus-corpuscles. The relation between the size of the pus-corpuscles and that of the epithelia from the convoluted tubule is always the same—that is, the latter are one-third larger than the former. If the pus-corpuscle happens to be small in the case examined, the kidney epithelia will be small, but if large, the epithelia will be larger. The comparative sizes of the different smaller formations found in the urine are illustrated in figure 59. The smallest corpuscles with double contour, and which are not granular, are the red corpuscles; the next in size, being the smallest granular corpuscles, are the pus-corpuscles; then follow the smallest epithelia found in urine, one-third larger than the pus-corpuscles—the epithelia from the convoluted tubules of the kidney. Finally, the next larger epithelia are shown, always twice the size of the pus-corpuscles, which are those from the ureter or from the prostate gland, between which no difference can be noted. If this relationship is kept in mind, no mistake can be made, though it must be remembered that when an individual small epithelial cell is found, the diagnosis cannot be positively made until they are compared with the pus-corpuscles."

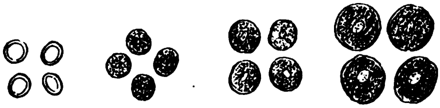


Fig. 59.—Corpuscles and epithelia, showing their comparative sizes.

The epithelia from the straight collecting tubules are less frequently seen, and occur in larger numbers only in the severe forms of nephritis. They are about the same size as the cuboidal, but narrower.

Kidney epithelia may occur in clusters or in cast-like groups.

The clinical significance of the presence of renal epithelia is not always appreciated. They are indicative of renal inflammation, and when casts are absent, as is often the case, they assist in making the diagnosis of nephritis. Renal epithelia are also present in suppurative conditions of the kidney, and, in combination with pus and cells from the pelvis, assist in making the diagnosis of pyelonephritis. It is very important, therefore, to look for epithelia one-third larger than pus-corpuscles whenever a renal affection is suspected.

Epithelia from the urethra present a great variety of shapes and sizes, as the mucosa is of the stratified type. In the milder inflammations of the urethra the cells are flat or cuboidal and of considerable size, although smaller than those from the bladder. In the more intense inflammations and ulcerations—as, for instance, in strictures—the irregular columnar epithelia appear. Cells from the prostatic portion are dense, granular, round, pyriform, or irregular, about one and one-half to twice the size of a leukocyte.

Epithelia from the Prostate.—These are cuboidal or columnar, the latter derived from the duct of the gland. The cuboidal epithelia are twice the size of pus-cells, and identical in appearance with those from the ureter, but larger than those from the kidney. If these epithelia are present in large number, while renal and pelvic epithelia are absent or few in number, the cells of ambiguous size are undoubtedly prostatic and not ureteral. The accompanying presence of other prostatic elements (mucus-plugs, spermatozoa, etc.) also assists in the diagnosis. Prostatic epithelia may be found in the urine after coitus, after massage of the prostate, and in the sediment of urine in cases of prostatic inflammation and prostatic abscess.

Epithelia from the ejaculatory ducts and seminal vesicles may also be found in the urine, and are of the columnar ciliated variety. The cilia may become broken, but the character of the cell can be made out from the delicate striation of rods along the upper surface. These cells are smaller and narrower than those from the bladder. Cells from the *vesicles* are of medium size, round, highly granular, dense, with an ill-defined nucleus, and often contain spermatozoa. These epithelia may be found in the urine in cases of vesiculitis, tuberculosis of the vesicles, etc., and after massage of the vesicles.

Epithelia from the Vagina.—These are the largest found in urine. Those from the upper layers are flat; from the middle layers, cuboidal; from the deepest layers, columnar. The flat variety is present in most urines in women in health. They are increased in leukorrhea, and may be present in masses, accompanied by bacteria, mucus, and granular matter. They may be shrunken and folded, and may contain fat-globules, which have no significance. They have very pale, fine granulations. The cuboidal epithelia in the middle layer are seen in vaginitis in considerable numbers, and in chronic cases contain fat-granules. The columnar epithelia are seen in ulcerations and deep-seated inflammations. All these vaginal cells are larger than those of the corresponding layers in the bladder.

Epithelia from the Uterus.—These are not so frequently found in the urine, but should be remembered, as they may give rise to confusion. Epithelia from the cervix are flat, cuboidal, or columnar, usually irregular in shape, and smaller than those in the vagina. They are practically identical with the irregular epithelia from the urethra, and can hardly be differentiated. Epithelia from the mucosa of the uterus are tall, columnar, ciliated, of delicate structure, and may be accompanied by ciliated pus-corpuscles. Their presence indicates endometritis.

Extraneous Epithelia.—In both normal and pathologic urines scales of epidermis in the form of flat, horny cells from the genitals (prepuce, clitoris, and labia) are often present. They are recognized by their zigzag contours, by the absence of nuclei, the presence of fat-globules and dust-particles, their pallor, and their shriveled condition.

CASTS.

True casts of the kidney were first described by Henle in 1842, but they had been seen by Vigla, Quevenne, and Rayer in the years 1837 to 1840 in France, and by Simon and Nasse in 1842 in Germany. The first detailed description was given in 1867 by Rovida. Casts may be defined as cylindric bodies which represent the molds of the uriniferous tubules of the kidney. The origin of renal casts is still unsettled. At one time they were considered as the product of secretion of the epithelia of the tubules, or as masses of transformed or disintegrated epithelia. Later on their production was ascribed to the transudation of coagular elements of the blood, which pass into the tubules as a result of lesions in the walls of the latter, solidify in the lumen, and are voided with the urine. This last view is probably more close to the correct solution of this question than the other, and casts are probably the products of an exudation from the blood-vessels with the admixture of fragments of epithelia.

One serious defect in this theory, which has not yet been remedied or explained, is the fact that undoubtedly there are cases in which casts are present in the urine without any albumin being detected by chemic means. A number of such cases are on record, but it is possible that in these cases there was a very small quantity of albumin which escaped detection (Heitzmann).

Clinical Significance.—Casts have been found in renal congestion, jaundice, anemia, nervous diseases, and gastro-intestinal affections *without any renal inflammation.* Their presence, according to von Jaksch, does not in itself imply renal disease. If casts be admitted to constitute products of an inflammatory process, it is improbable that they can occur without any renal disease, yet at least one variety—the pure hyaline—is found in almost every urine, both in health and disease. In order to make a diagnosis of renal disease it is always important to weigh separately each microscopic element found in the sediment as a part of the evidence, and to base our judgment upon the particular combination of factors which are found in each case. There is no question but that the presence of casts is one of the most important of these factors, and one of the most useful in localizing and differentiating renal disease.

Classification of Casts.—The following table (Ogden) shows a useful classification of tube-casts:

- I. Hyaline (transparent) casts:
  - (1) Pure hyaline.
  - (2) Fibrinous.
  - (3) Waxy.
- II. Granular casts: . . . .
  - (1) Fine.
  - (2) Coarse.
  - (3) Pigmented.
- III. Epithelial casts.
- IV. Fatty casts.
- V. Blood-casts.
- VI. Pus-casts.
- VII. Crystalline casts:. . . . .
  - (1) Urate.
  - (2) Oxalate.
  - (3) Cystin.
- VIII. Bacterial casts.

Hyaline Casts.—There are three varieties of hyaline casts: (1) Pure hyaline; (2) fibrinous; (3) waxy.

Pure Hyaline Casts.—These are pale, delicate, transparent, homogeneous cylinders, varying in diameter and in length, usually with rounded ends and parallel and straight sides, but sometimes indented, twisted, serpentine in shape, with ragged ends. It is very difficult to detect pure hyaline casts, except by constant focusing with the fine adjustment of the microscope and by diminishing the amount of light in the field. Pure hyaline casts occasionally contain some very fine pale granules, or here and there show upon their outlines a blood-cell, a leukocyte, a droplet of oil, etc. Such casts are still in the hyaline class. The source of the hyaline casts may be to a certain extent deduced from their diameter. The smaller, narrower casts arise from the convoluted tubules, while the larger ones come from the straight or collecting tubules.

The mode of origin of hyaline casts is still unsettled. According to Rovida, they are the products of secretion by the tubular epithelium, but experiments on animals made by Ribbert show that they are probably due to the exudation of albumin within the tubules. Whatever may be their origin, the mere presence of pure hyaline casts must not lead to the hasty conclusion of the existence of renal disease, for they are found in practically every specimen of urine.

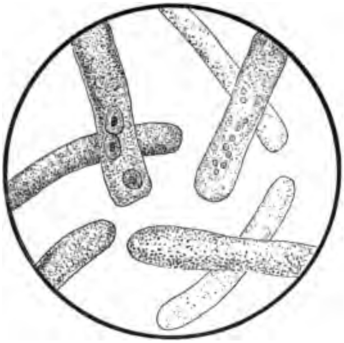


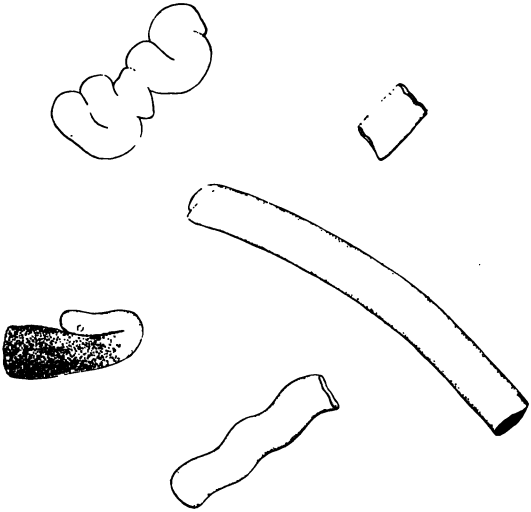
Fig. 60.—Hyaline casts.

Hyaline casts are commonly found, however, in a great many diseases and disturbances of the kidney, especially in chronic interstitial nephritis, in amyloid kidney, and in passive congestion. In acute nephritis and in active congestion they are most numerous. They may be the only indications of a severe nephritis, and, on the other hand, these casts are met with in the urine of persons with healthy kidneys in whom no albuminuria or any other sign of renal inflammation had ever been observed. To find hyaline casts we use, in preference, fresh urine, and sediment it, instead of centrifuging.

Fibrinous casts are dense, highly refractive, transparent, and of a yellowish color which ranges between pale yellow and deep brown. Like pure hyaline casts, they vary in shape and size, but are, as a rule, larger than the average hyaline cast. They should not be confounded with *waxy* casts, which are always perfectly colorless. The term fibrinous casts is inappropriate, as they have nothing to do with fibrin and are suggestive only by their yellow color. Like pure hyaline casts, they may be studded with fine granules and may have adhering blood or fat-droplets. Their presence indicates an acute disease or disturbance in the kidneys, and fibrinous casts are, as a rule, seen only temporarily during the acute stage of these conditions. They are not unfavorable signs in the prognosis.

Waxy Casts.—These casts are very highly refractive and always perfectly colorless and transparent. They are usually large in diameter, and vary in shape like the pure hyaline. They may be studded with coarse granules, and may have adhering the same elements as the pure hyaline casts. They are so dense that they may look cracked or broken into segments, with irregular ends. They are never present in active congestion and in acute nephritis, but are found in advanced stages of chronic nephritis, both interstitial and parenchymatous. They are of bad prognostic significance, as a rule. They are often seen in amyloid infiltration of the

PLATE 7



FIBRINOUS CASTS (*Ogden*).

kidneys, and in this condition are of some diagnostic value, although not pathognomonic, as they occur in other chronic diseases of the kidney. It must be remembered, however, that the term "waxy" is misapplied to these casts, as they show the "amyloid reaction" with methyl-violet and potassium iodid and iodin solution, in the absence of amyloid degeneration, and, on the other hand, this reaction is absent in some cases when this degeneration exists.

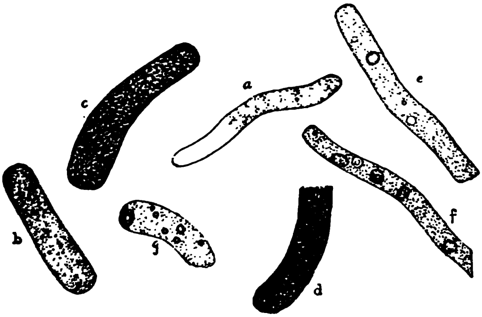


Fig. 61.—*a*, Hyaline and finely granular cast; *b*, finely granular cast; *c*, coarsely granular cast; *d*, brown granular cast; *e*, granular cast with normal and abnormal blood adherent; *f*, granular cast with renal cells adherent; *g*, granular cast with fat and a fatty renal cell adherent (Ogden).

All the other casts to be described are practically modifications of the hyaline cast, which forms the groundwork upon which various elements adhere or into which they become imbedded. A hyaline cast covered with granules is a *granular cast;* one covered with epithelia is an *epithelial* cast, etc.

Granular casts consist of a hyaline basis in which fine, coarse, or pigmented granules are imbedded. These granules probably come from the disintegration of renal epithelia, or partly from the destruction of blood-cells. The pigmented granules, also called "brown granules," probably derive their color from blood-pigment. Granular casts may be stained yellow or brown by bile.

These casts vary considerably in dimension, and are often broken, the end often being concave or zigzag. Sometimes they show fragments of epithelial cells and transition-forms which prove that the granules are derived from the epithelia, and that granular casts are degenerated forms of epithelial casts. They may be found in any inflammatory condition of the kidney, and do not indicate any particular disease of this organ. Their presence is about equally significant with that of renal epithelia as evidence of nephritis.

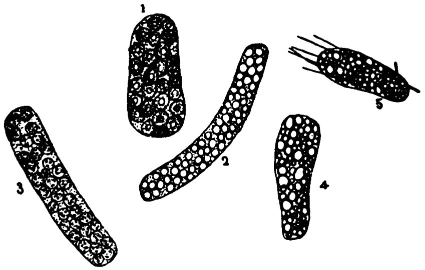


Fig. 62.—1, Epithelial cast; 2, blood-cast; 3, pus-cast; 4, fatty cast; 5, fatty cast with a compound granule and fatty renal cell adherent (crystals of the fatty acids protruding) (Ogden).

Epithelial Casts.—When a cast is entirely covered with renal epithelium, it is called an epithelial cast. The basis of this formation may be either hyaline or granular, and the cells may be imbedded or only adherent. When only one or two cells adhere to a hyaline cast, the term "hyaline with adherent epithelium" should be used. The outlines of the cells are not always distinguishable, but their nuclei usually stand out prominently. The cells may contain fat-globules, and leukocytes may adhere to these casts along with the epithelium.

Perfectly formed epithelial casts appear in urine under such conditions only as cause the separation of renal epithelium in the entire circumference of a renal tubule. They always indicate an active inflammatory process in the parenchyma of the kidney, and "their presence alone suffices to establish the existence of acute nephritis or the supervention of a fresh paroxysm in that disease" (von Jaksch). The intensity of the inflammatory process is in proportion to the number of these casts. They are rarely found in chronic and interstitial nephritis and in amyloid kidney. Epithelial cylinders with a lumen may be seen in cases of great congestion in which the lining of the tubules is thrown off unchanged.

Blood-casts.—These casts consist of a hyaline or granular base covered with red blood-cells or of cylinders of coagulated blood (fibers) with imbedded blood-cells. The occurrence of blood-casts indicates a hemorrhage into the tubules. According to the length of time which these casts have remained in the tubules the blood-cells on them may be normal or abnormal (*cf.* p. 255).

Blood-casts are found in the renal hematuria due to tuberculosis, stone, tumor, etc.; in acute nephritis, acute congestion, and hemorrhagic infarcts of the kidney. Their presence simply shows the existence of renal hemorrhage, and not necessarily of renal disease.

Fatty casts are cylinders which are thickly studded with fat-droplets and granules. The term does not apply to hyaline or granular casts which show one or two oil-globules. They occur in short, highly refracting cylinders, and may show bristling, needle-like or hair-like crystals of fatty acids. The minute fat-drops are highly glistening, and should not be confounded with granules which have a duller luster.

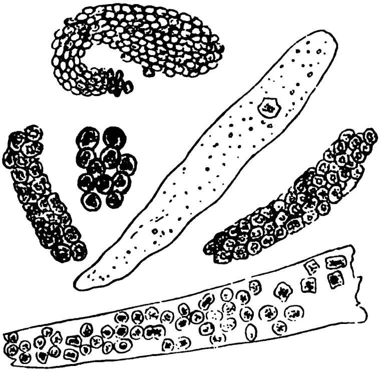


Fig. 63.—Blood-casts, composed wholly of red or white corpuscles, or hyaline substance covered with blood-corpuscle.

These casts were first discovered by Knoll, and are usual in protracted cases of chronic nephritis with a tendency to fatty degeneration of the kidney (von Jaksch). Fatty degeneration, it must be remembered, shows an advanced stage of alteration in the renal cell. Fatty casts are also found in the fatty stage of acute nephritis, and occasionally in severe renal congestions (Ogden).

Pus-casts are hyaline or granular cylinders covered with pus-cells or leukocytes. They are often confounded with epithelial casts because the pus-cells are often so granular that the nuclei are obscured. The addition of dilute acetic acid dissolves the granular matter and shows the nuclei of the leukocytes.

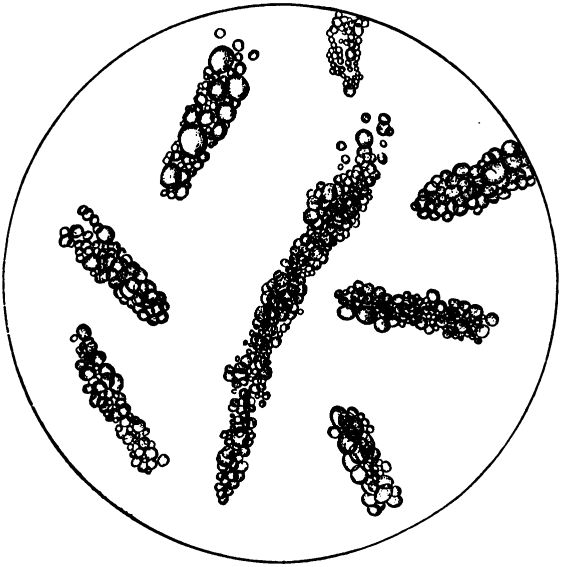


Fig. 64.—Fatty casts (after Peyer).

Pus-casts are not met with, except in a chronic suppurative process in the kidney, such as an abscess, tuberculosis, and chronic pyelonephritis. In cases of chronic pyelitis or pyelonephritis there may be casts from the pelvis, calices, or from the straight tubules, consisting of large and irregularly shaped plugs of coagulated material covered with pus-cells. In acute non-suppurative nephritis and in acute exacerbations of chronic nephritis there may be hyaline or granular casts, with a few adherent pus-cells, but these do not constitute true pus-casts.

Crystalline Casts.—These are simply hyaline or granular casts to which crystals or amorphous granules of a chemic sediment are adherent or in which these are imbedded. A *urate cast* is one covered with crystals of ammonium urate, usually of the characteristic spheric shape. The *cystin* cast is rarely seen in cystinuria, and is covered with cystin crystals. The *calcium oxalate* casts are covered with the crystals of this substance. *Amorphous urates*, when present in large amounts, may oat hyaline or other casts and obscure their true orphology. In such cases it is important to dis-

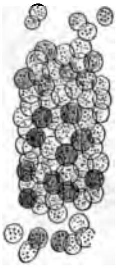


Fig. 65.—Casts formed of leukocytes from a case of acute nephritis (von Jaksch).

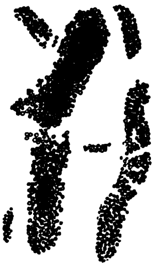


Fig. 66.—Casts of urates from a case of emphysema (von Jaksch).

solve the urates in warm water, as has been described on page 240.

Bacterial casts are cylinders covered with bacteria, but masses of germs that resemble these casts, and that sometimes are seen in urine undergoing decomposition, do not constitute bacterial casts. The latter are sometimes confounded with the pigmented or brown granular casts, but resist the action of acetic acid and strong alkalis. Bacterial casts are rare, and usually indicate renal suppuration or renal embolism.

FALSE CASTS OR CYLINDROIDS.

False casts, mucus casts, or cylindroids are occasionally found in urine, and seem to be pure mucus molds of tubules. Their true chemic nature is not exactly known, but they have little clinical significance and are frequently present without any albumin. They are smooth, long, flat, transparent, finely fibrillated, with indistinct, wavy, longitudinal striations, and have tapering ends. They are characterized especially by their great length, and are often twisted or folded. The chief interest in false casts is their resemblance to true casts, and they must be carefully distinguished by means of the peculiarities just described. Occasionally, epithelia or other elements may adhere to them and increase their resemblance to true casts.

False casts are found usually wherever there is irritation of the bladder and lower urinary passages which has extended up to the kidneys. They are also found in urine of very high specific gravi it must be remembered that they are not identical with mucus threads, although chemically mucus-casts and mucus-threads are probably the same.

MUCUS-THREADS.

Mucus-threads appear in normal urine in the form of more or less opaque, ropy masses of irregular shape, but sometimes in the form of long and transparent shreds, the ends of which taper or split in fine divisions which fade away imperceptibly. They are often covered with amorphous urates, and may be mistaken for casts. They are, however, flat, and not cylindric; generally very much narrower than casts,

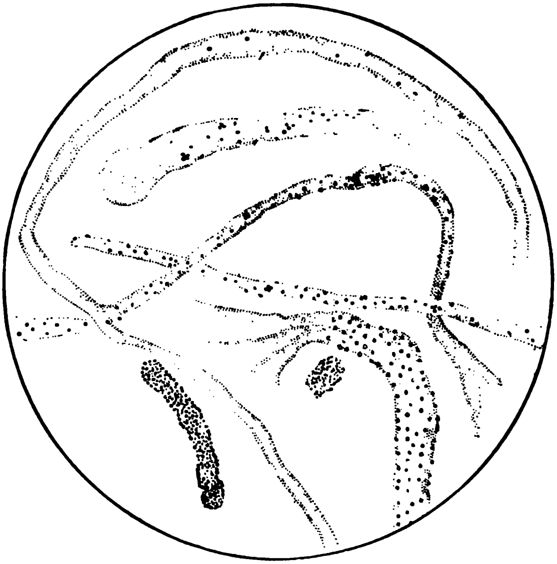


Fig. 67.—False casts (after Peyer).

and their granules can be dissolved with a little heat on the addition of acids or alkalis. The presence of these threads has no very marked clinical significance unless there is an excessive amount of mucus, which indicates irritation or inflammation in some part of the genito-urinary tract. Mucin threads may be demonstrated by the addition of a little acetic acid and a little solution of iodin, potassium iodid, tartaric acid, or dilute mineral acids, but an excess of the latter will redissolve the mucin. Mucin threads may be found in urine without addition of acids, being probably precipitated by the action of acids formed in acid fermentation. The greater the irritation in the genito-urinary tract, the more opaque, the thicker, and the more ropy becomes the mucus, and appears then in the form of clouds mixed with epithelial cells from the seat of the trouble. The mucus-corpuscle which appears in urines rich with mucus has already been described on page 265.

PROSTATIC PLUGS.

Prostatic plugs are large, colorless or yellow molds of the prostatic ducts (Fig. 70), cylindric, with rounded ends, or of irregular shape. Their outlines are not sharply defined, as they generally are found in clouds of mucus, but their chief characteristic is the fact that they have imbedded in them or adherent to them spermatozoa and epithelial cells from the prostatic ducts. Their presence indicates an inflammation of the prostate involving the ducts, and they are especially seen in urines after massage of the prostate.

AMYLOID BODIES.

Amyloid bodies, or *corpora amylacea*, are minute bodies which are found in the acini of the prostate, and occasionally are found in the urine, especially after massage of a prostate in the state of chronic follicular prostatitis. The word "amyloid" is a misnomer, as these bodies have nothing to do with starch chemically. They are more or less opaque, rounded bodies, of either homogeneous or lamellated structure. Their central portions consist of a darker or more densely lamellated core. They are not affected by hot water nor dissolved by strong nitric acid; they are colored red with methyl-violet, while starch takes a blue color. Amyloid bodies, when treated with iodin, often show a violet color which becomes blue on the addition of sulphuric acid. They are said to occur normally, and their clinical significance is doubtful. In old men larger masses of these bodies may occur, visible to the naked eye and surrounded with a mixture of phosphates to form the so-called prostatic concretions which form in the follicles of the prostate.

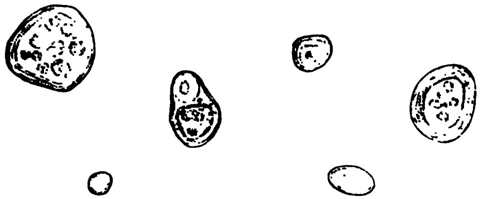


Fig. 68.—Corpora amylacea from the urine (Ogden).

SPERMATOZOA.

Spermatozoa are bodies about 50 μ in length, consisting of an oval head, a minute body, and a long, delicate, whip-like tail (Fig. 69). In fresh semen they show active eel-like movements, but in urine they are usually motionless. They require a high power for their detection and fine focusing for their demonstration. In the urine they may be accompanied by mucus, prostatic plugs, amyloid bodies, and by epithelia from the prostate, the vesicles, and the neck of the bladder; also by pus-cells and by spermatic crystals. The latter are identical with the so-called spermin crystals, also found in sputum, blood, and feces, and are narrow, tapering, and diamond-shaped.

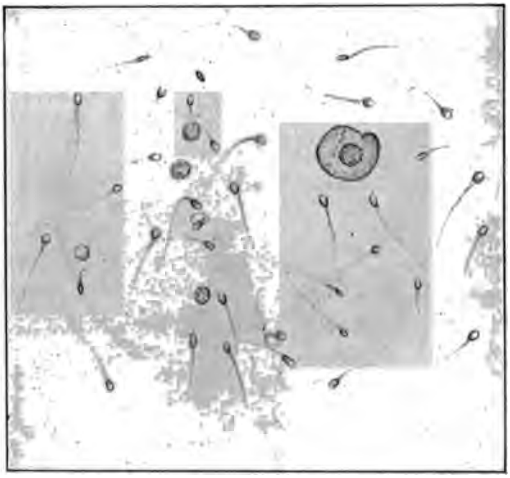


Fig. 69.—Spermatozoa in urine (Ogden).

Clinical Significance.—Spermatozoa are found frequently in the urine of healthy men and of both sexes after coitus. They are found also in men after nocturnal emissions, and sometimes in the urine in acute fevers, sepsis, and convulsions. Their most important clinical bearing is in cases of *spermatorrhea*, when they are constantly found in the urine, and also in cases of acute and chronic prostatitis and seminal vesiculitis, or of congestion or irritation of the prostatic region. The presence of an inflammatory condition in cases in which spermatozoa are found may be inferred from the coëxistence of mucus, pus, epithelia from the region concerned, and from the broken tails and immovable condition of the spermatozoa.

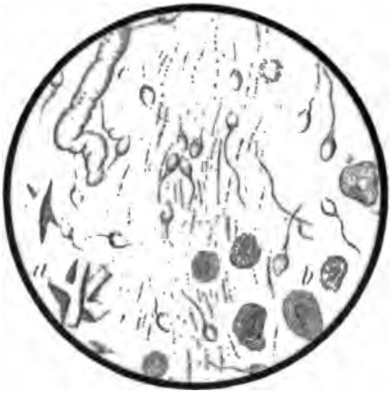


Fig. 70.—Spermatozoa. At *a* are so-called Böttcher crystals; at *b*, amyloid bodies; at *c*, a prostatic plug (Jakob).

The detection of spermatozoa is important from the medicolegal aspect in cases of *suspected rape.*

It is easy to show their presence in vaginal secretion, and stained linen may be soaked in either water or salt solution and the sediment examined. A chemic reaction which may aid in their recognition was described, in 1897, by Florence, of Lyons. A few drops of the suspected fluid are treated with a drop of Florence's reagent, which consists of:

Potassium iodid	1.65 gm.
Iodin	2.64 "
Distilled water	30.00 "

This reaction is probably dependent on the presence of cholin. If semen is present, small, dark, rhombic crystals appear, resembling closely the hemin crystals described in Teichmann's test for blood.

MICRO-ORGANISMS.

The urine may contain bacteria, molds, or yeasts. Fresh urine is said to be sterile in normal persons if obtained directly from the bladder, but is contaminated in transit by the bacteria always present in the urethra.

If urine is allowed to stand in the air for some time, it becomes turbid from *masses of bacteria* of the non-pathogenic variety. The conversion of urea into ammonium carbonate is probably produced by several bacteria, of which the **Micrococcus ureæ** (Fig. 71) is the most important. This germ is found very frequently on the surface of decomposing urine, and occurs in chains of round, highly refracting

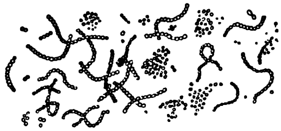


Fig. 71. — Micrococcus ureæ (after von Jaksch).

dots. It is constantly present in the air. Large varieties of other bacteria which take part in the decomposition of the urine have been described.

Molds are not seen normally in decomposing urine, but often occur in diabetic urines floating on the surface. A variety of molds may be found in urines which have been allowed to stand in uncovered vessels.

Yeasts.—The beer-yeast fungus is found in diabetic urine or in urine contaminated accidentally with sugar. It occurs in oval, transparent cells, free or in groups of three or more, and multiplies rapidly in acid urine, but ceases to grow when it becomes alkaline. They should not be mistaken for red blood-cells, and are distinguished by their oval shape and the presence of a cell-body without a focal point.

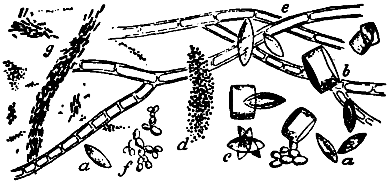


Fig. 72.– Sediment from fermenting diabetic urine with casts of micrococci: *a*, *b*, *c*, Various forms of uric acid; *d*, micrococci in form of casts; *e*, molds; *f*, yeast fungi; *g*, bacilli and micrococci (after von Jaksch).

The **Sarcina urinæ** is found occasionally in urine, resembles the sarcina of the lung, and occurs in cubes of eight cells each arranged like a bale of goods.

Pathogenic Bacteria.—Of these, a large number have been found in urine. In a great variety of the suppurative conditions of the urinary tract the bacteria of pus-formation are found—Streptococcus pyogenes; Staphylococcus pyogenes albus, citreus, and aureus. In many specific diseases, as in typhoid fever, anthrax, glanders, erysipelas, and tuberculosis, the germs of these affections are found in the urine.

The most important germs found in urine, for diagnostic purposes, are the *colon bacillus*, the *gonococcus*, and the *tubercle bacillus*.

The **colon bacillus** plays an undoubted rôle in urinary infection, but, unfortunately, its study is complex and must be left to trained bacteriologists.

Gonococcus.—The gonococcus of Neisser is the specific agent of gonorrhea, and is a diplococcus, consisting of groups of kidney-shaped cocci with a flattened surface facing each other. They are found in the discharge from the urethra in gonorrheal urethritis, and it is characteristic of them that they occur within the bodies of the pus-cells. It is often very difficult to demonstrate gonococci in urine. For this purpose the specimen must be chosen from the portion of urine which contains most pus and threads, preferably after massage of the prostate and vesicles, and must then be centrifuged, the thickest part of the sediment spread on several slides, and allowed to dry in the air. It is then fixed by heat by passing the slides very slowly three times through the flame of an alcohol-lamp, and stained with a solution of methylene-blue. A thin part of the specimen where there are pus-cells must be sought, and the slides carefully gone over to find the characteristic diplococcus within the pus-cells.

Inasmuch as there are germs in the urethral discharge which resemble the gonococcus very closely, the true germs of gonorrhea may be distinguished by *Gram's method*, as follows:

(1) Cover the slide with anilin-gentian-violet solution without heat for thirty seconds; (2) wash in water; (3) cover with Gram's solution of iodin (iodin, 1 part; potassium iodid, 2 parts; water, 250 parts) for thirty seconds; (4) wash with 95 per cent. alcohol until the color ceases to come out; (5) wash in water; (6) counterstain with saturated aqueous solution of Bismarck-brown for ten seconds; (7) wash in water; dry; mount in balsam, and examine with an oil-immersion lens. The gonococci are stained brown, while other diplococci are stained bluish-purple by this method.

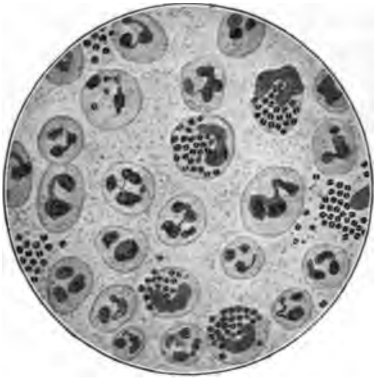


Fig. 73.—Pus from gonorrhea, showing gonococci (Jakob).

Gram's solution decolorizes the gonococci, and they afterward take the brown color from the counterstain.

It is in chronic gonorrhea, with scarcely any discharge excepting a morning drop and a few shreds, that gonococci are looked for in the urine. Wherever there is a sufficient discharge, the germs should be looked for in the pus. The absence of the gonococcus from the urine is of no conclusive negative value, as the germ may be deeply lodged in the follicles of the prostate or the urethra.

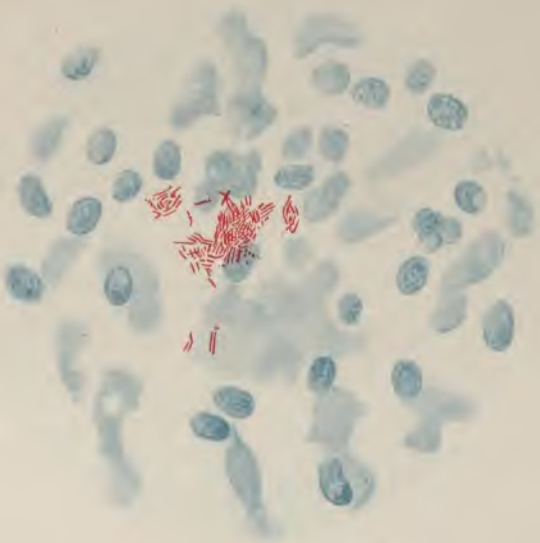
The Tubercle Bacillus.—It is still more difficult to discover the tubercle bacillus in the urine. For this purpose it is important that the urine should be fresh, and preferably it should be obtained by catheter after thoroughly cleansing the external genitals, and examined at once. In this manner we prevent its destruction by decomposition, and also avoid the admixture of the smegma bacillus, which is found on the prepuce and glans, and which resembles the tubercle bacillus very closely.

The sediment should be centrifuged, the supernatant liquid decanted, and the sediment washed two or three times with distilled water, decanting each time; again centrifuged, and the sediment spread on a number of cover-glasses by means of a pipet. The spreads must be very thin, and should be fixed by gentle heat. They are then stained with carbolfuchsin for two minutes over the flame, care being taken not to allow the stain to evaporate. They are next decolorized in 20 per cent. nitric acid, washed in water, and then further decolorized in 70 per cent. alcohol. It must be remembered that too much acid cannot be used; that it is important to decolorize thoroughly, and that alcohol should be poured on the slide until no more pink color comes off, and until the preparation by reflected light assumes a delicate, grayish-pink tint. The slides are then stained with aqueous solution of methylene-blue; dried; mounted in balsam, and examined with a one-twelfth oil-immersion lens. The acid and alcohol decolorize smegma bacilli, but do not affect the tubercle bacilli, which remain stained by the fuchsin, while the other germs, pus-cells, etc., are stained blue. The tubercle bacillus is recognized by its characteristic form and grouping. It occurs in long, thin rods, slightly curved or bent, and often crossed and arranged in parallel formation. Its ends are slightly clubbed, and it presents a series of unstained vacuoles.

Special Methods of Isolating the Tubercle Bacillus from Urine.—Even with the greatest care the above-described method often fails to isolate the tubercle bacillus, the germs being few in number and greatly diluted in the urine, evading search in the sediment. A number of new methods have recently been suggested to obviate this difficulty. While these methods are still in the experimental stage, the results already obtained with them indicate that they or their subsequent modifications are destined to play an important rôle in the detection of tubercle bacilli in the urine.

These methods are all based on the principle that if some coagulable substance be added to the urine, it will carry with it in coagulation all the tubercle bacilli present, and when this coagulum is again

PLATE 8



TUBERCLE BACILLI IN URINARY SEDIMENT; × 800. (*Ogden.*)

dissolved by digestants, the bacilli will again be set free and may be obtained from the dissolved substance by centrifuging. The simplest of these methods is that of Vos, who in 1896 added egg-albumen to urine, allowed it to coagulate, separated the coagulum, and digested it with artificial gastric juice. Another and a more convenient method is that of Jusset, which involves the use of blood plasma. The latter is added to the urine, and the mixture is heated to 100° C. The coagulum is then digested with artificial gastric juice. The solution is centrifuged, and smears are prepared in the usual way from the sediment. In this manner tubercle bacilli have been found in urines in which they could not be detected by ordinary methods.

An improved method of fixing the smears for staining has been lately suggested by Maragliano. The sediment is taken up with a platinum loop and spread upon a slide upon which a drop of a solution of albumin and glycerin had been previously placed. The addition of albumin and glycerin as a mounting medium is especially useful when the sediment, as sometimes happens, does not contain any pus to speak of and consequently is not easily fixed on the slide.

Finally, injections of portions of the sediment of a urine suspected of containing tubercle bacilli into guinea-pigs offer a useful means of diagnosis. The lesions obtained in these animals, however, take some time to develop, and a negative result, even in these animal experiments, is not always conclusive.

The absence of tubercle bacilli in an ordinary microscopic examination of the sediment is by no means decisive in diagnosis, and tuberculous lesions may exist in the kidneys or elsewhere in the genito-urinary tract without any discharge of tubercle bacilli into the urine. (See Part IV, p. 322, Tuberculosis of the Kidneys, etc.)

PARASITES.

It is very rare to find parasites in the urine, and a detailed description of these must be sought in works on pathology. The following parasites have been found in urine on rare occasions:

Filaria sanguinis hominis, the parasite of chyluria, discovered by Lewis, of Calcutta, and found in the blood and urine of persons passing a milky urine.

Distoma hæmatobium, a form found in eastern South Africa, whose eggs may infect the urinary passages, the veins, etc. They produce a sharp pain when they are passed along the urethra, and the urine contains blood, pus, fat, and the eggs of distoma.

Echinococcus.—The hooklets of Tænia echinococcus are found in urine in cases of parasitic cysts in the kidney, or in cases of rupture of such cysts into the urinary tract from some neighboring organ.

Ascarides.—The presence of these worms in the urine may be due to the accidental washing-away of one of these parasites from the region of the anus, or to an abnormal communication between the intestine and the urinary tract.

How can the intensity of a cystitis be judged by the character of these cells? What is meant by an endogenous pus-corpuscle?

Describe epithelia lining the *pelvis*. What does their presence indicate?

Describe the two types of cells from the *ureter*. When are they present in sediments?

Describe a typical *renal epithelial cell*. What does their presence indicate? What two forms are distinguished and where do they come from?

How are renal epithelia distinguished from other cells of similar appearance?

What do epithelia from the straight collecting tubules indicate?

What is the clinical significance of renal epithelia?

What is the appearance of *urethral epithelia?* Of those from the deeper layers? From the prostatic portion? From the *prostate?* The ejaculatory duct? The vesicles?

Casts.—Define casts. What are the theories of their origin?

What is the relation of casts to albumin?

What is the clinical significance of casts and when have they been seen without renal disease?

Name the principal classes of casts.

Describe a *pure hyaline* cast. What may be concluded from the size of these casts? What is their mode of origin? What do they indicate?

Describe *fibrinous casts*. What do they indicate and what is their prognostic value?

Describe a *waxy cast*. In what conditions are they found? What is their prognostic meaning?

Define a *granular cast*. Where do the granules come from? What do they indicate?

Define an *epithelial cast*.

What term is used when only a few epithelia adhere to a cast?

What does the presence of epithelial casts show?

What are epithelial cylinders with a lumen?

Define a *blood-cast*. What does their presence indicate? When are they found in the urine?

Define *fatty casts*.

What variety of casts may be mistaken for fatty casts? When are these casts found?

Define *pus-casts*. What do they indicate?

What varieties are found in pyelitis?

PART IV.

DIAGNOSIS OF URINARY DISEASES.

CHAPTER XXI.

CHARACTERS OF THE URINE IN DISEASES OF THE KIDNEY AND RENAL PELVIS.

In the foregoing pages the methods of examination and the clinical significance of the various normal and abnormal constituents of the urine have been detailed. In applying this knowledge to diagnosis the student's chief concern will be the recognition and differentiation of the various diseases of the kidney. In doing so he will meet the difficulty of deciding as to the *particular lesion* which is present in the kidney, and as to *what stage* the process has reached. Unfortunately, each renal disease, though clearly defined pathologically, *does not present a separate and distinct type of urine.* Not only this, but two or more types of lesions may be present in the same kidney at the same time, and may obscure each other to a certain extent so that only repeated examinations, the careful elimination of all external factors influencing the constitution of the urine, and the scrupulous weighing of each element in the findings, will lead to a correct diagnosis. In the following summary, which is necessarily brief, are bile irritate the kidney in their transit and considerable amounts of sugar often cause congestion. This condition is also observed in strictures, enlarged prostate, and other obstructive diseases of the urinary tract; in operations on the urethra, bladder, etc. In itself acute congestion is a transient condition, but is chiefly interesting because it often precedes acute nephritis.

The urine varies according to the degree and duration of the congestion. In mild cases it may be normal, except a few red cells, a few hyaline casts, a few renal epithelia, and a small amount of albumin. The quantity is usually increased at first; the acidity may be normal; the specific gravity may be somewhat lowered, and the total solids somewhat reduced.

In severe cases the urine changes completely. It is usually high-colored, reddish or smoky, and contains visible amounts of blood. The quantity is small—sometimes less than 300 c.c. The acidity is increased; the specific gravity is usually higher than normal. The total solids are increased. Albumin is always present—sometimes in considerable amounts for a day or two. A few hyaline and finely granular casts, blood-casts, red cells, renal epithelia, and crystals (these causing irritation) are found in the sediment. In acute congestion that has lasted some time we find fatty renal epithelia; occasionally small fatty casts and fat-globules; some pus-cells, pelvic epithelia, etc., showing the extent and severity of the process. Acute congestion is differentiated from acute nephritis chiefly from the transitory nature of the signs in the urine. Albumin is usually present in small amounts, and the casts are few in number. They appear suddenly and diminish rapidly. The urine just before death in chronic interstitial nephritis resembles that of acute congestion, except that its specific gravity is low and the solids reduced.

CHRONIC CONGESTION.

Chronic or passive congestion is always secondary to a disturbance of circulation due to disease of the heart, arteries, or the liver, or to tumors of the abdomen, or to pregnancy.

The urine is diminished in quantity in uncomplicated cases. Its color is usually high, brownish red, but if diuretics have been given or if the patient is in a bad state of nutrition, it may be pale. It is generally somewhat cloudy, owing to increase of urates and mucus, and as a rule strongly acid in reaction. The specific gravity is typically high, but may be normal or low in pale urines. The absolute amount of solids is diminished, especially if there is dropsy. The relative amount of solids is increased, except in extreme cases of dropsy. There is usually a slight trace or a trace of albumin; occasionally albumin is absent and the degree of congestion does not correspond with albuminuria. The sediment contains a few small hyaline casts, with occasional red and white blood-cells adherent and a few free red cells, although blood is often absent. In pregnancy the urine is lighter, of a lower specific gravity, and occasionally contains much albumin, without any cor plication in the shape of nephritis. In such cases we must look out for convulsions. The urine of chronic congestion is diagnosed from that of chronic interstitial nephritis by the low specific gravity, the small amount of urea, and the predominance of urine passed at night in interstitial nephritis. The two urines are difficult to distinguish from each other in interstitial nephritis near death, when the quantity is practically normal.

ACUTE DIFFUSE NEPHRITIS.

Acute nephritis, acute diffuse nephritis, and acute Bright's disease are the names applied to an acute degenerative or inflammatory process in the kidneys. The causes of this condition include those mentioned as producing acute congestion, and acute nephritis may be the sequel of an acute hyperemia. The most frequent cause is some acute infectious fever, such as scarlatina, diphtheria, pneumonia, typhoid fever, and influenza. Sudden and violent exposure to cold sometimes operates as a cause, and occasionally the acute inflammation follows extensive burns, erysipelas, and other local affections of the skin. Acute nephritis may also occur in women during pregnancy, and in these cases convulsions are usually present.

According to Councilman, acute diffuse nephritis includes a number of pathologic processes, any one of which may predominate, or be exclusively present, or be combined with other lesions in the list: (1) Acute degeneration of the kidney; (2) acute glomerular inflammation; (3) acute hemorrhagic inflammation; (4) acute interstitial inflammation.

Characters of the Urine.—The *quantity* is diminished at times to an extreme degree, and at the height of the disease it may be reduced to a few ounces. If the disease loses its acute character, the quantity increases, but during the acme of the disease there may even be suppression, which, if it lasts long, may be considered fatal.

The *specific gravity* varies with the quantity and increases to 1025, 1030, or even higher during the acute stage of the disease, while during convalescence it becomes lower with the increased volume.

The *color* also varies with the quantity voided and with the amount of blood, but the typical urine of this disease is dark-brown, approaching chocolate in color, smoky, opaque, and dull in luster. During convalescence the urine gradually clears up and becomes lighter. The *reaction* is always highly acid, except when large amounts of alkaline salts are given in the treatment. Of the normal constituents, the *urea* and the *chlorids* are diminished in quantity, and the *total solids* (actual) are correspondingly reduced. The relative amount of solids, however, varies with the volume excreted, and in the early stage, when the urine is very scanty and concentrated, this amount may be normal or high. During convalescence the amount of urea and chlorids increases, but during the acme of the disease the urea is often reduced to 100 grains, or even less, for twenty-four hours (Purdy).

There is always a large amount of *albumin*, usually from 0.5 to 1 per cent. by Esbach's method. It is in these cases that the urine coagulates on heating, so that it appears almost solid, whence the erroneous expression of "100 per cent. of albumin" has arisen. In rare cases albumin is absent throughout the disease. In a few cases it is present intermittently, and in some cases it appears suddenly toward the acme of the disease. The amount of albumin decreases toward convalescence.

The amount of *blood* in the urine in acute diffuse nephritis varies considerably, both in different individuals and in different periods of the disease. Usually it appears early and disappears before the albuminuria vanishes. The amount of blood and the amount of albumin are valuable prognostic indications, and the sudden increase of albuminuria and hematuria shows a relapse of the disease.

The *sediment* is usually copious and brownish or reddish, owing to the presence of blood, urates, and a large amount of coloring-matter. The predominant element under the microscope is the red blood-cell, which is usually present in considerable numbers, and appears in the abnormal form (see p. 256), unless the hemorrhage is very marked. There are always some pus-corpuscles in moderate numbers; epithelium from the renal tubules is always in evidence, and may be present in large numbers. There may be a few caudate cells from the pelvis or some cells from the calices.

Hyaline and finely granular casts, coarsely granular, epithelial, blood, and fibrinous casts are usually present in considerable numbers, together with masses of granular débris from broken-down cells.

If the disease goes on after the acute stage subsides, it enters into the so-called *fatty stage*, which is characterized by fatty renal cells and fatty casts, the number of which depends upon the severity of the preceding acute stage. During the convalescent stage the characters of the urine become gradually normal, the sediments show fewer casts, fewer renal cells, and fewer blood-cells, until there may be only a trace of albumin, a few hyaline and granular casts, and an occasional blood-cell or renal cell. This urine is identical in microscopic features with that of acute congestion. If complete recovery takes place, the urine becomes normal. Acute nephritis very often becomes chronic, and during the convalescence there may be relapses or exacerbations in which the urine again shows the features of the acute stage.

Differentiation.—In mild acute nephritis it is not always easy to differentiate from severe acute congestion by examining the urine alone. We must rely chiefly on the persistence of marked albuminuria, of a considerable amount of blood, and of many casts.

The second stage (fatty stage of acute nephritis) may be mistaken for subacute parenchymatous nephritis complicated by an acute process. In the latter the acute complication will gradually subside, leaving the disease in its original form. In the subacute condition the amount of albumin is usually larger, and the total amount of urea is much lower than in the acute cases.

CHRONIC DIFFUSE NEPHRITIS.

(Chronic Nephritis with Exudation; Chronic Glomerular Nephritis; Chronic Arteriosclerotic Nephritis; Chronic Parenchymatous and Interstitial Nephritis.)

This disease either follows acute nephritis or develops as a chronic condition from the start. In this condition the lesions are both parenchymatous and interstitial, and each of these two varieties of lesions is represented in the characters of the urine, which vary according to the predominance of either the parenchymatous or the interstitial element. It is well for the student, therefore, to understand the changes in the urine which characterize each of these distinct sets of lesions. Interstitial lesions give rise to an increased quantity, a pale color with a low specific gravity, and a diminution of the relative and absolute solids, especially of urea. The parenchymatous lesions are represented by a comparatively large amount of albumin and the presence of renal casts and of renal cells in various stages of fatty degeneration. The rule is that in chronic diffuse nephritis the interstitial changes predominate, but this is by no means always so.

The causes of chronic diffuse nephritis are the same as those of the acute form, and the chronic type is often the sequel of acute nephritis; but it is well to remember that chronic diffuse nephritis is more apt to develop from acute nephritis due to scarlet fever, diphtheria, pneumonia, or other infectious diseases.

Characters of the Urine.—The *quantity* is diminished, as a rule, but not so markedly as in acute nephritis, and the daily amount fluctuates much more markedly than in the acute form. In the late stages, when the interstitial changes gain the ascendency, the volume increases. The *specific gravity* varies with the quantity, but is usually low—at least below 1020, and in the later stages it is often below 1010. The *color* is variable, but generally light, the urine being often cloudy, owing to the presence of a large amount of sediment.

There is always some *albumin*—sometimes a large amount, up to 1 per cent.; but the average is between $\frac{1}{8}$ and $\frac{1}{4}$ of 1 per cent. The amount of albumin fluctuates, and seems to be in fairly constant relation to the specific gravity. It generally increases for a time, but in the later stages, tending toward the interstitial type, the amount of albumin often becomes reduced. The *total solids* are more or less diminished, although there may be a temporary increase of solids when dropsy subsides under diaphoretics. *Urea and chlorids* are below the normal, and *indican* is either normal or increased. The most important features of the urine are found in the *sediment*. The latter is abundant, and contains numerous casts of practically all types. The characteristic casts are, however, the so-called fatty casts, which indicate an advanced chronic parenchymatous lesion. In the earlier stages these fatty casts are few, and the hyaline, faintly granular, and epithelial casts predominate. In the more advanced cases the fatty casts become more numerous, and they are accompanied by casts with dark and prominent granules and by broad casts from the large straight tubules. In addition to casts, the sediment contains many renal cells, some of which are fatty, but usually no blood is seen unless there is an acute exacerbation. A few pus-cells are usually seen. Connective-tissue shreds are always present, and a fair number of large shreds may be seen in the sediment. Pelvic epithelia, ureteral and bladder epithelia may also be present, but are not characteristic. In advanced cases waxy casts may be found, sometimes in large numbers, and as the interstitial lesions increase, the sediment becomes more and more scanty, the casts and renal epithelia fewer, and the fatty elements less numerous.

CHRONIC PARENCHYMATOUS NEPHRITIS.

(Subacute or Chronic Glomerular Nephritis; Fatty Degeneration of the Kidneys; Chronic Diffuse Nephritis of the Parenchymatous Type; Chronic Degeneration of the Kidney.)

This is a chronic disease of the parenchyma of the kidney, characterized by marked changes in the glomeruli and the epithelial lining of the renal tubules. The vascular tufts of the glomeruli are swollen, the number of cell nuclei in them is increased, and the glomerular blood-vessels are degenerated and become obliterated. The capsule of the glomerulus shows proliferation of epithelium and new connective-tissue growth. The tubular epithelium is extensively diseased, necrosed, and becomes detached. There are edema and proliferation of connective tissue to a minor extent in the intertubular tissue.

This condition often accompanies chronic diseases,—*e. g.*, syphilis, tuberculosis, malaria, etc.,—but it may be a sequel of acute nephritis—*e. g.*, after scarlet fever. In such cases it is at first subacute and later becomes chronic. Chronic parenchymatous nephritis may occur in old persons, and in some cases without discoverable cause. It is one of the possible sequels of heart disease and of other disturbances of circulation (emphysema, pleuritic effusions, etc.) such as cause chronic congestion.

Characters of the Urine.—The urine varies at different stages of the disease. During *the active stage*, or during acute exacerbations, when there is marked dropsy, the *amount* of urine is scanty, the *color* high or bloody, the *reaction* markedly acid, the *specific gravity* high—up to 1035. The *solids*, especially urea and chlorids, are low, on account of dropsy, but relatively there is an increase of urea unless there are interstitial changes setting in strongly. A very large amount of *albumin* is present,—up to 3, 4, or even 5 per cent.,—but the average is 0.75 per cent. The reddish or dark *sediment* is abundant, contains urates, hyaline, granular, and fatty casts, and fatty epithelia from the kidney. In advanced cases one finds waxy casts. Blood-cells and leukocytes are also usually present.

During the *inactive, chronic stage* the dropsy and edema are diminished or disappear, and the *amount* of urine increases, being about normal. The *specific gravity* is slightly lowered, the *solids* are diminished, though the chlorids may be higher than in the active stage (absorption of dropsy). Less *albumin* is present, but there is still a considerable amount. An abundant *sediment* is found to contain the same elements, but fewer casts and fewer renal epithelia and blood-cells are found.

During the final stage the *kidneys become atrophic*, and the urine, while about normal in *amount*, is very low in *specific gravity*, contains but little albumin, and a scanty sediment consisting largely of fatty elements and waxy casts.

Differentiation.—*Subacute cases* (subacute glomerular nephritis) are noteworthy for the great frequency with which acute exacerbations occur in the inactive stage. In these exacerbations the urine resembles that of acute diffuse nephritis, with the fatty elements in prominence and with a marked proportion of blood-cells and blood-casts. Such cases cannot be distinguished from the second (fatty) stage of acute nephritis except by the clinical history. The symptoms and urinary changes of an acute diffuse nephritis are transient, those of a subacute or chronic parenchymatous nephritis, more or less permanent.

From chronic diffuse nephritis subacute and chronic glomerular nephritis may be distinguished not only by the clinical history, but by watching the quantity of urine voided. If this be permanently increased, the condition is chronic diffuse nephritis. The two exceptions to this rule are: (1) Cases of chronic diffuse nephritis during acute exacerbations, when the amount is often reduced. (2) Cases of ease is not exactly known. Possibly it results from the irritation due to the excessive amount of uric acid eliminated. Syphilis and chronic malaria are known to be accompanied often by chronic interstitial nephritis, though the exact connection between these diseases and nephritis is not known. Arterial disease (arteriosclerosis) produces changes in the arteries of the whole body which are identical with those found in the arteries of the kidney, and there is a distinct causal relation between arteriosclerosis and interstitial nephritis. In connection with uranalysis, the chief thing to be remembered about the lesions of chronic interstitial nephritis is that they are very insidious and take years to develop, and that in the early stages a diagnosis is often impossible unless the urine be carefully watched from day to day and repeatedly examined. The lesions of interstitial nephritis consist chiefly in the growth and increase of connective tissue in the stroma of the kidney, and secondarily in changes in the glomeruli and tubules. The study of the urine must be pursued bearing these facts in mind.

Characters of the Urine.—The typical urine of chronic interstitial nephritis is increased in quantity, usually perfectly transparent, and paler than normal in color, with a markedly acid reaction and a rather low specific gravity. Albumin is present in small quantities, or it may be absent. Very few casts are seen in the sediment, chiefly of the small hyaline variety. The chlorids are not markedly changed in amount, the phosphates are reduced, and the urea is more or less diminished.

The *quantity* is usually increased until the last stage, when heart-failure sets in, and the urine is secreted in smaller amounts. A diminution of the quantity is, therefore, a bad sign in chronic interstitial nephritis. The *specific gravity* is lowered in proportion to the extent of the interstitial changes, but it is never so low as in chronic diffuse nephritis or in amyloid kidney. Usually it ranges between 1010 and 1015. In the last stage, after heart-failure, the specific gravity rises somewhat. There is some difference of opinion as to the frequency of *albuminuria* in this condition. According to Purdy, the reason why albumin is so often found absent in this disease is that the albuminuria is intermittent. It is probable that very slight traces are always present, even in the early stage. The amount of albumin is always small, unless the interstitial nephritis becomes complicated by transient acute conditions. In the last stages—in heart-failure—the albumin increases, but it never reaches the extreme limit which is seen in chronic diffuse and chronic parenchymatous nephritis.

The amount of *urea* diminishes from the first, and this reduction is proportionate to the extent of the interstitial lesions. The *phosphates* are also very constantly reduced, but the *chlorids* do not suffer reduction to any extent. The *total solids* are greatly diminished, both absolutely and relatively.

The *sediment* contains few or no red *blood-cells*, but a moderate number of pus-cells, some containing fat-globules and granules; *epithelia* from the renal tubules, some of which are fatty; and, in severe cases, columnar epithelia from the straight collecting tubules are present in small numbers (Heitzmann). *Crystals of hematoidin* in the form of rust-brown needles and plates, either free or within the pus-cells or epithelia, may be found, indicating the chronic nature of the disease and denoting a previously existing hemorrhage. *Connective-tissue shreds* of various sizes are often noted. *Casts* from the renal tubules in this disease are rarely found in large numbers, and often they are difficult to detect. They are of the hyaline type or of the finely granular, and come usually from the narrow tubules. *Crystals* of uric acid and of calcium oxalate may be seen, especially in the early stages. The sediment as a whole is quite scanty, and even after centrifuging, very little is obtained, so that its study is not so easy as in the other renal diseases.

When acute exacerbations of nephritis occur, the urine presents the altered characters which would be expected in an acute process. The quantity of albumin becomes increased and the sediment resembles that of acute nephritis.

AMYLOID KIDNEY.

(Waxy Degeneration; Lardaceous Kidney.)

This is a chronic condition of the kidney which is usually the expression of amyloid degeneration in various organs of the body. It may be met with in syphilis, tuberculosis, chronic bone disease, and chronic wasting diseases. It is frequently mistaken for chronic diffuse nephritis, although it is very important to distinguish these conditions, as the emaciated and cachectic persons who have amyloid degeneration require treatment entirely different from that applicable in chronic diffuse inflammation of the kidney.

Characters of the Urine.—The amount is increased, the color lighter than normal, but the transparency remains unaltered. The specific gravity is low, and there is a well-marked reaction for albumin in the typical cases. Besides serum-albumin there is usually a considerable amount of globulin. The sediment is usually scanty, and contains but few cells and a moderate number of casts, of the hyaline, granular, or, occasionally, the waxy variety.

It is still a matter of discussion whether *waxy casts* are characteristic of amyloid disease and consist of amyloid material. Amyloid material in tissues is distinguished by its reactions to certain stains, but it is very difficult to stain casts with these dyes. The sediment is washed repeatedly by decantation with diluted glycerin, and a little methyl-violet solution is added. Both waxy and hyaline casts will assume a light reddish tint. (*Cf.* p. 280, Waxy Casts.)

Amyloid degeneration may be complicated by parenchymatous degeneration as the result of interference with the renal nutrition. When this takes place, the urine will resemble that of diffuse nephritis so closely that it cannot be differentiated. The above description applies to typical urine of amyloid. There are certain variations, according to the stage of the process and the severity of the lesions. The *amount* of urine continues increased as a rule, but there are often periods of temporary reduction in volume, accompanied by attacks of diarrhea. When the *specific gravity* is comparatively high (1016 to 1118), the prognosis is more favorable, but in the average case it is low, and may even reach 1004 in the late stages. In the early stage of the disease the amount of *albumin* is usually small, then it increases, and toward the end it may again decrease, with a marked polyuria. The *solids*, especially the urea, decrease in proportion to the lesions and to the low state of nutrition. In the late stages the *casts* are very few, hyaline, and usually of comparatively large size.

Differentiation.—It is almost impossible to differentiate amyloid kidney from chronic interstitial nephritis, unless we admit that waxy casts are characteristic of the former, and this has not yet been settled. The clinical symptoms are usually our chief guide, and it must be remembered that amyloid changes frequently occur along with chronic interstitial nephritis. In fact, according to Heitzmann, amyloid degeneration is only a secondary affection found in chronic nephritis.

TUBERCULOSIS OF THE KIDNEY.

This may be primary, but more frequently it is an accompaniment of tuberculosis in other organs. It may result from the extension of tuberculosis from the lower part of the urinary tract. In order to understand the various features in the urine of tuberculous kidneys, it must be remembered that, in addition to the formation of tubercles, there is and contains small cheesy lumps. Microscopically, the chief features are pus, with usually smaller amounts of blood; numerous renal cells in various stages of degeneration and fatty change; occasionally large hyaline and granular casts, which may be covered with blood-cells when there is an acute exacerbation of the process, or an intermittent hematuria. If the pelvis and calices are involved, there appear large clumps of pus, mucus, and débris, which may be recognized as casts of the calices.

The chief diagnostic feature of the urine in these cases is the presence of the tubercle bacillus in the sediment. The detection of this germ has already been considered on page 297. When the tubercle bacillus is absent, we cannot exclude tuberculosis of the kidney, because this germ may not appear in the urine until late in the disease. In cases of doubt we must look for some other focus of tuberculosis, and we may use tuberculin injections for diagnostic purposes, or inject portions of the sediment into the peritoneal cavity of a guinea-pig.

STONE IN THE KIDNEY.

The effect of stone in the kidney upon the urine is three-fold: (1) In cases of stone uncomplicated by inflammatory conditions there is an increase in the chemic elements which constitute the stone—*e. g.*, uric acid, calcium oxalate, etc., both in the urine itself and in the sediment. (2) When inflammation ensues, due to the irritation produced by the stone or to secondary infection, either ascending or hematogenous, then there are, in addition, the established, the urine shows the features of pyelonephritis. There is an abundant sediment of pus, more or less blood, and crystalline elements or concretions, but the latter may not be present. The urine is very turbid, and is either faintly acid or alkaline. Its specific gravity is low; the normal solids are diminished; there is a considerable amount of albumin, owing to the presence of pus and of a complicating nephritis. The sediment contains chiefly pus-cells, often in clumps; shreds of connective tissue; renal epithelia, also in clumps, mixed with pus and mucus; and red blood-cells in moderate numbers. Casts may be present, but may be obscured by the pus.

Differentiation.—It will be seen that the urine in the earlier stages is rather characteristic, and whenever we find the signs of congestion, hemorrhage, and an unusually abundant sediment of crystals in urine immediately on voiding, the presence of stone in the kidney may be thought of seriously. In the later stages, with suppuration setting in, the differentiation of stone from tuberculosis; from tumor of the kidney, or from pyelonephritis presents serious difficulties. The finding of tubercle bacilli, on the one hand, and of tumor elements, on the other, differentiates from tuberculosis and from stone. The passage of small concretions or masses of crystals, when seen soon after voiding, are significant of stone also in this stage, but there are undoubtedly cases in which the examiner must content himself in the suppurative stage of stone with a diagnosis of pyelonephritis "possibly due to stone."

TUMORS OF THE KIDNEY.

Of these, the malignant growths, sarcomata and carcinomata, are interesting in their relations to urine. Sarcoma is the more common, and is met with in young persons. Malignant tumors of the kidney usually are slow to develop, but when they have reached a certain stage, they grow rapidly and lead to death in a year or two. The disease may be unilateral, especially in primary cases.

The Urine.—In malignant tumors of the kidney more or less blood is always found—occasionally large amounts of fresh blood, when there is a paroxysm of hematuria. Albumin is present in the urine in large or smaller quantities, according to the amount of blood and the state of the renal parenchyma. Acetone is frequently found in the urine in cancer of the kidney. The amount of urine is usually increased unless the ureter is blocked. The specific gravity and the solids are altered, according to the extent of the renal destruction, the involvement of the opposite organ, and the presence of congestion or inflammation of the kidneys. As in stone of the kidney, the urine is changed, not only owing to the presence of the disease itself, but also owing to the accompaniment of nephritis, and, in the later stages, the breaking-down of the tumor, the ulceration and the suppuration which ensue, especially when there is secondary infection and when the malignant disease invades the renal pelvis. The sediment of a case of malignant tumor presents the features, in the early stages, of simple acute congestion of the kidney. Later, when the ulcerative changes take place, the urine shows the features of chronic pyelitis already mentioned under the heading of Stone.

Differentiation.—It is very difficult to make a diagnosis of renal malignant tumor from the urine alone, as the only real characteristic features of such urines is the presence of portions of the tumor with their distinct alveolar structure. These are found very rarely. The presence of single tumor-cells, even in considerable quantities, is not of much value, as they may not appear till the pelvis is involved, and as the cells themselves do not present any definite diagnostic features.

CYSTS AND CYSTIC DEGENERATION OF THE KIDNEY.

Cystic degeneration of the kidneys is a congenital condition characterized by a conglomeration of cysts of various sizes occupying the renal tissue. The entire kidney may be destroyed. It is almost always bilateral.

Solitary cysts of various sizes may occur in the kidney as the result of the blocking of a tubule or of the capsule of Bowman. In chronic interstitial nephritis it is common to see small single cysts of this kind.

The diagnosis of congenital cystic disease is rarely made during life. Greatly enlarged kidneys; a hypertrophy of the left cardiac ventricle, and increased arterial tension are the chief diagnostic guides. Large single cysts may give rise to palpable tumors.

ACUTE PYELITIS AND PYELONEPHRITIS.

Pyelitis is an inflammation of the pelvis of the kidney. Pyelonephritis is a combined inflammation of the kidney and the renal pelvis. Acute pyelitis often complicates acute nephritis. It may be due to an extension of the disease from the kidney; to infection from below, from the bladder, or to irritation due to stones or concretions. Pyelitis alone, without nephritis, is usually due to the last-named cause.

The urine in acute pyelitis resembles that of acute nephritis in all respects, save that it contains more pus-cells and a large number of epithelia from the pelvic lining. When acute nephritis is associated with pyelitis, renal epithelia and casts are prominent in the sediment, and the relative importance of the coincident nephritis may be judged from this. When pus is present in considerable amounts, the term "acute suppurative pyelitis" may be used.

CHRONIC PYELITIS AND PYELONEPHRITIS.

The same remarks apply to the relation of chronic pyelitis and chronic nephritis. In chronic (non-suppurative) nephritis there may be a certain amount of chronic pyelitis, shown by a few pelvic cells in the sediment, but it is the suppurative forms of chronic pyelitis and pyelonephritis that are clinically interesting. Chronic suppurative pyelitis may be due to the irritation of stones, to tuberculosis, or to tumors of the kidney or pelvis or both; to infection through the blood in fevers; to obstruction of the ureter due appears when the kidney is replaced (intermittent hydronephrosis).

The urine presents at first the signs of acute congestion, as the opposite kidney takes up the work of both. The quantity is markedly diminished, the solids somewhat lowered, and there may be some albumin. Hyaline casts, a few blood-cells, and a few renal epithelia may be seen in the sediment.

When hydronephrosis intermits—*i. e.*, is relieved—there is a sudden polyuria, with sometimes an increase in the amount of albumin and blood. The contents of the hydronephrotic sac are practically water with a slight amount of urinary salts, a trace of albumin, and a few red and white blood-cells and epithelia from the kidney and pelvis.

PYONEPHROSIS.

Pyonephrosis is an accumulation of purulent urine in the renal pelvis and renal cavity, due to an obstruction of the ureter, together with infection. It may follow a hydronephrosis when infection supervenes, or it may develop from an acute or chronic pyelitis when the ureter becomes obstructed. The causes of ureteral obstruction are the same as in hydronephrosis. The kidney is gradually destroyed and atrophies, forming finally a large abscess cavity.

The urine shows the signs of an acute or active congestion, due to the overwork of the opposite kidney when the obstruction is absolute. In such a case there is no pus, and the diagnosis cannot be made from the urine alone.

When the obstruction is relative, or if it is removed suddenly, there is a considerable flow of pus, and the urine assumes the characters described under Chronic Pyelonephritis. It is turbid, with an abundant greenish-white sediment, consisting of pus, epithelia from the kidney and pelvis, connective-tissue shreds, and blood (slight amounts usually), together with fragments of stone (when stone is present) and larger débris of kidney tissue. There is usually a considerable amount of albumin and a marked proportion of globulin.

URETERITIS.

Inflammation of the ureter alone is rare, and is scarcely ever diagnosticated, certainly not from the urine alone. Catheterization of the ureter may, however, reveal ureteritis, stricture of the ureter, calculi impacted in this canal, etc.

Ureteritis may form part of pyelitis or cystitis by extension, or may result from the irritation due to the passage of a calculus with sharp points. It may follow compression of the ureter by tumors from without, strictures, or kinks of the ureter. Tuberculous ureteritis may occur when the kidney or the bladder is similarly diseased.

The urine in a simple ureteritis is that of acute renal congestion, with high color, high specific gravity, and small amount of albumin and blood. The sediment shows blood, pus (few cells), and the characteristic cells of the ureteral lining.

CHAPTER XXII.

CHARACTERS OF THE URINE IN DISEASES OF THE LOWER URINARY TRACT AND OF THE GENITAL ORGANS.

CYSTITIS.

Acute Cystitis.—This is an acute inflammation of the bladder, caused by infection with the gonococcus or with some pus-producing germ, usually by an extension of infection from elsewhere in the tract or by the use of dirty instruments. Acute cystitis also results from exposure to cold and wet; sexual excesses; acute urinary retention; the use of irritant drugs (copaiba, cantharides); or injury to the bladder. It may also occur as a complication of infectious diseases.

The urine is diminished in amount, as a rule. It is bloody or smoky, strongly acid, with a high specific gravity and relatively high solids. The amount of albumin varies with that of blood and pus. The sediment contains fresh blood, pus, mucus, mucus-threads, and many epithelia from the superficial layers of the bladder.

Chronic Cystitis.—This may follow an acute cystitis and be due to the same causes. A common cause of chronic cystitis is an enlarged prostate or some other form of urethral obstruction. In these cases the urine cannot be voided completely, and stagnates in the bladder, inducing cystitis. The same takes place in paralysis of the bladder. In tumors, stone, or tuberculosis of this organ there is usually a chronic cystitis. Between the vagina and the bladder there may be fistulas communicating which induce cystitis.

The urine is not markedly affected in quantity; usually pale and cloudy or bloody, with an ammoniacal or putrid odor, and thickened in consistence (mucus). In the early stages it may be highly acid, but later becomes alkaline. The albumin depends on pus and blood. An abundant thick and heavy sediment is present, chiefly of pus; of cells from all the layers of the bladder epithelium; of mucus, amorphous phosphates, triple phosphates, and ammonium urate.

Differentiation of Pyelitis and Cystitis.—The detection of numerous epithelia from the pelvis, on the one hand, and from the bladder, on the other, does not always suffice to make a distinction between pyelitis and cystitis. In fact, very well-trained observers have been misled into regarding a specimen of urine in a case of pyelitis for one due to cystitis alone. In view of the great importance of this differentiation the recent researches of Rosenfeld, extending through a number of years, are of interest. Rosenfeld found that the urine of a pyelitis differs from that of a cystitis in several important respects, which may be briefly summed up as follows:

1. The *reaction* of the urine in pyelitis is almost always acid. An alkaline reaction is never found

in uncomplicated pyelitis. An alkaline reaction, therefore, speaks for cystitis, while an acid reaction does not exclude cystitis. The reaction must be observed in freshly voided urine.

2. In pyelitis the pus-cells are characteristically ragged and distorted in contour. In cystitis they are characteristically round and uniform in shape. The distinction should be drawn only when large numbers of pus-cells show either of these types. The finding of round forms does not exclude pyelitis necessarily, but testifies to the presence of cystitis.

3. The *red blood-cells* from a pyelitis are "abnormal,"—*i. e.*, washed out, altered in form,—while in cystitis, except when due to tumors, they are fresh and "normal." This does not apply to hemorrhages other than microscopic.

Pus.	Cystitis—Albumin Per Cent.	Pyelitis—Albumin Per Cent.
I. Maximum degree: Numerous pus-cells in liter-glass . .	0.1	0.3
II. Moderate degree: Pus sediment about ½ cm. high.	0.6	0.2
III. Slight degree: Pus sediment from 1 to 2 mm. high.	Just distinctly recognizable.	0.1
IV. Minimum degree: Recognizable almost only by the microscope	Not recognizable.	Distinctly recognizable.

4. The *ratio of albumin to the amount of pus* is the most important point. In cystitis there may be great amounts of pus, but the albumin never ex-

ceeds from 0.1 to 0.15 per cent. In pyelitis, however, the amount of pus may be very small, as appears from the thickness of the sediment, but from 0.1 to 0.15 per cent. of albumin and over will be found, and when the pus is abundant, the albumin reaches higher amounts—up to 0.3 per cent. The table on p. 336, according to Rosenfeld, approximately shows this ratio (Brooks).

TUBERCULOUS CYSTITIS.

Tuberculosis of the bladder is usually secondary to that of other organs of the genito-urinary tract. The first stage—of productive lesions (tubercles) in the bladder—does not give marked changes in the urine, while the second, marked by ulceration and by complicating chronic cystitis, gives a rather characteristic urine.

The urine is diminished in amount, pale or bloody, and turbid, usually acid in reaction, with a low specific gravity and diminished normal solids. The albumin varies with the amount of blood and pus present, and may be abundant during attacks of hematuria. The sediments consist of large amounts of pus, bladder epithelia, and blood-cells. The presence of tubercle bacilli and the presence of ulcers seen in an examination of the bladder with a cystoscope are conclusive evidences of tuberculous cystitis. The absence of tubercle bacilli from the urine does not, however, necessarily exclude the presence of this disease.

TUMORS OF THE BLADDER.

Of the benign tumors in the bladder, the most common are papillomata, but fibromata and fibromyxomata also occur. Papillomata are diagnosticated in the urine from the presence of masses of villous growths of microscopic size in the sediment. In malignant growths of the bladder the urine

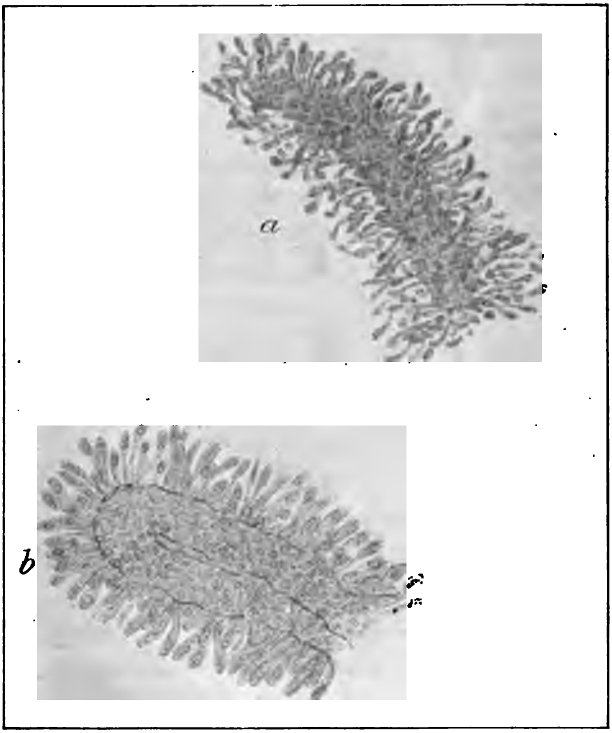


Fig. 74.—Portions of a villous growth of the bladder: *a*, Magnified 190 diameters ; *b*, magnified 370 diameters (Ogden).

presents the same features as in chronic cystitis, but its reaction is usually acid, and there is apt to be more blood and even large blood-clots. Shreds of tissue and portions of the tumor may be found in it. Cells resembling those of the new growths are also sometimes seen in the sediments, but no positive diagnosis can be made from their presence. The cystoscope and exploratory operations are often required for diagnosis, but the urine alone often points to the presence of bladder growths.

STONE IN THE BLADDER.

The diagnosis of stone in the bladder is not usually made from the urine alone. Sounds, the lithotrite, and the stone-searcher are used as aids, as well as the *x*-rays and the cystoscope.

The urine presents the characters of acute or chronic cystitis, according to the length of time the stone has been in the bladder, and the shape and size of the stone. Small concretions and an unusually abundant sediment of a crystalline or amorphous deposit, such as uric acid, calcium oxalate, etc., are sometimes clues to the diagnosis.

PROSTATITIS.

Acute prostatitis is an acute parenchymatous inflammation of the prostate gland. It is caused by infection aided by congestion (exposure to cold and wet, sexual excitement, urethral stricture, traumatism, passage of calculi). The chief infectious agent is the gonococcus, which enters the prostatic ducts from the posterior urethra in cases of gonorrheal urethritis. During an attack of gonorrhea acute prostatitis may be excited by a variety of causes, chiefly by sexual intercourse, alcoholic indulgence, instrumentation, etc.

Characters of the Urine.—Acute prostatitis is often accompanied by a congestion of the kidneys, and in such cases the urine gives the signs of renal hyperemia, with a high or bloody color, high specific gravity, scanty amount, and a trace of albumin. The urine may, however, show none of these signs except a diminished amount and a little blood. Microscopic examination reveals many red blood-cells, pus-cells, epithelia from the prostate and its ducts and from the seminal vesicles; spermatozoa, most of which are dead and have broken tails; and plugs from the prostatic ducts. These are distinguished from renal casts only by their larger size and less regular shape, and the fact that they have spermatozoa adherent to them, embedded in them, or attached to them. They are dense, less transparent than hyaline casts, and show a coating of granular matter. The pus-cells are not greatly altered, as a rule, and the epithelium is fairly fresh.

Chronic prostatitis may follow the acute form or may be chronic from the start, due to sexual overindulgence, masturbation, or coitus interruptus. It may also result from chronic urethral obstruction —*e. g.*, by strictures, narrow meatus, phimosis, etc. —or from irritation or injury to the prostate by passing stones.

Characters of the Urine.—Unless kidney lesions be present at the same time, the urine is not very arkedly changed in chronic prostatitis. It is usually pale, acid, turbid, with slightly lowered specific gravity and an amount of albumin varying with the amount of pus. In the sediment we find large numbers of pus-cells, chiefly in masses, mixed with a mucous substance; many epithelia in various states of disintegration and fatty change from seminal vesicles, the prostate, its ducts, and the neck of the bladder. There are rarely many blood-cells, but spermatozoa are in evidence, free and embedded in masses of pus, epithelia, and mucus. These masses often assume the shape of casts and plugs, already described under Acute Prostatitis. Shreds of connective tissue, mucus, and round-cells, massed together with adherent spermatozoa and pus-cells, are also often found in this condition. Amyloid bodies (see p. 290) are sometimes found in considerable numbers, but usually only a few are present. They assist in the localization of the trouble in the prostate. The presence of an accompanying cystitis will give its signs, already described.

TUBERCULOSIS AND CANCER OF THE PROSTATE.

Tuberculous prostatitis is almost always a part of a tuberculous process in some other genito-urinary organ. The urine does not differ essentially from that which characterizes chronic prostatitis, except that its sediment on centrifuging (or after massage, on standing) contains tubercle bacilli. Several examinations are often needed to find these germs. (See Tubercle Bacillus, p. 297.)

Cancer of the prostate is rare, especially the primary form. The urine is practically that of chronic prostatitis, with an occasional hemorrhage. The presence of cells with large round nuclei from the tumor cannot serve for a positive diagnosis, but in conjunction with clinical signs may hint at cancer.

SEMINAL VESICULITIS.

Inflammation of the seminal vesicles occurs as the result of the same causes as prostatitis. Acute seminal vesiculitis is a complication of gonorrheal urethritis. The chronic variety occurs with or without prostatitis as a sequel to gonorrhea, stricture, etc., and from such causes as congestion, over-indulgence in sexual intercourse, masturbation, etc.

The diagnosis of seminal vesiculitis is usually made by palpating the vesicles. **The urine in** the acute form shows pus-cells, blood, epithelia from the vesicles, numerous spermatozoa, shreds of vesicular lining, and plugs of coagulated matter from the vesicles. The signs of renal congestion may also be present. In the chronic form the urine shows, in addition to the signs of chronic prostatitis and chronic urethritis, masses of epithelia from the vesicles in a state of fatty change; spermatozoa more or less broken and distorted; plugs of coagulum, and shreds consisting of connective tissue; numerous round-cells, masses of mucus, and pus-cells.

SPERMATORRHEA.

In the functional disturbance known as spermatorrhea semen is found in the urine, especially after defecation. The discharge of thin, mucoid matter which follows or accompanies defecation contains many spermatozoa, some of which are alive. These structures may be stained with anilin dyes or may be tested with Florence's reaction. (See p. 293.) In addition, spermin crystals, fat-droplets, prostatic and vesicular cells, granular matter, and mucus are found in this discharge.

URETHRITIS.

In acute gonorrheal urethritis the urine is cloudy, acid, and deposits a sediment of mucopus, epithelia, and shreds from the urethra. With ensuing posterior urethritis there comes blood, in addition to these elements, in the shape of a moderate number of red cells. The amount of albumin depends upon the pus, and in other respects the urine is unchanged unless the kidney is affected.

In chronic urethritis the urine shows a much more scanty deposit of mucus and pus and usually a number of shreds from the urethra. The latter are whitish, translucent or opaque (yellowish if there be much pus), and microscopically show the presence of dense masses of coagulated material with débris of epithelia and pus-cells. There may be also epithelia from the urethra, free or in smaller masses, and occasionally some red cells and spermatozoa.

The diagnosis of specific urethritis is based upon the finding of the gonococcus. (See p. 295.) It is always best to seek this germ in the pus pressed out of the urethra or in the "morning drop" of chronic cases. In the urine the gonococcus must be looked for in the centrifuged pus or in shreds picked out with a pipet or a platinum loop.

QUESTIONS ON CHAPTERS XXI AND XXII.

1. *Acute Congestion of the Kidneys.*—What are its causes? What is the most frequent cause? Why is it chiefly interesting? What is the character of the urine? How is it distinguished from acute nephritis? From chronic interstitial nephritis just before death?

2. *Chronic Congestion of the Kidneys.*—What are the causes? Describe the urine. How is it distinguished from that of chronic interstitial nephritis?

3. *Acute Diffuse Nephritis.*—What are its causes? What pathologic processes may be present? Describe the characters of the urine. What do the amounts of blood and of urine indicate? What is the fatty stage? What other renal disease does it resemble?

4. *Chronic Parenchymatous Nephritis.*—What are its causes? Its lesions? Describe the characters of the urine in this disease. How is it differentiated from other forms of chronic nephritis?

5. *Chronic Diffuse Nephritis.*—What are its causes and lesions? Describe the urine of this disease. What are the characteristic casts in this form of nephritis? What changes in the urine indicate interstitial lesions, and what changes stand for parenchymatous lesions?

6. *Chronic Interstitial Nephritis.*—What are its causes? Its lesions? Describe the characters of the urine in this condition.

7. *Amyloid Kidney.*—What are its causes? Describe the chief characters of the urine. What is noteworthy of the quantity, the specific gravity, the solids, and the varieties of casts found?

8. *Tuberculosis of the Kidney.*—What elements in the lesions influence the characters of the urine in this disease? What is noted in the urine in early stages? In advanced stages?

9. *Stone in the Kidney.*—What three elements are at work in this disease in determining the characters of the urine? Describe the urine in the early stages; in the late stages, accompanied by infection.

10. *Tumors of the Kidney.*—What malignant growths occur in the kidney? Which is more common in children? What are the characters of the urine? On what should the diagnosis be based? What is the value of "cancer cells" in the sediment?

11. *Cysts of the Kidney.*—In what forms may cysts occur in the kidney? What symptoms lead to a diagnosis of congenital cystic degeneration? What does the urine show in cysts of the kidney?

12. *Abscess of the Kidney.*—Define renal abscess. What are its causes? What does the urine show before rupture? After rupture?

13. *Embolism of the Kidney.*—Define it. When does it occur? What changes in the urine are found in such cases?

14. *Acute Pyelitis and Pyelonephritis.*—Define each. What are the causes of acute pyelitis? What are the characters of the urine? How is acute pyelitis distinguished from acute pyelonephritis? What is suppurative pyelitis?

15. *Chronic Pyelitis and Pyelonephritis.*—Define each. To what is chronic suppurative pyelitis due? What are the characteristics of the urine?

16. *Cystitis.*—(*a*) *Acute.*—What are the causes and the characters of the urine?

(*b*) *Chronic.*—What are its causes? What are the features of the urine? How is pyelitis differentiated from cystitis? What is peculiar of the ratio of albumin to pus in cystitis? In pyelitis?

17. *Tuberculous Cystitis.*—What are the two stages of this disease and how do they show themselves in the urine? What does the absence of tubercle bacilli show?

18. *Tumors of the Bladder.*—What benign tumors occur in the bladder? Which is the most common? How are papillomata diagnosticated from the urine? What is the character of the urine in malignant growths of the bladder?

19. *Stone in the Bladder.*—How is it diagnosticated? What, in general, are the characters of the urine?

20. Describe the characters of the urine in *acute prostatitis;* in *chronic prostatitis;* in *tuberculosis of the prostate;* in *cancer of the prostate.*

21. What characteristics are observed in the urine of *seminal vesiculitis?* Of *spermatorrhea?*

22. Describe the sediment in the urine of *urethritis*—(*a*) acute, (*b*) chronic.

CHAPTER XXIII.

DIAGNOSIS OF THE FUNCTIONAL EFFICIENCY OF THE KIDNEY.

Within the past few years there have arisen certain new methods of urinary diagnosis which aim to determine the functional efficiency of the kidneys, or of one of these organs as compared to the other. The terms "sufficiency" and "insufficiency" as applied to the functions of an organ of the body were first used in relation to the stomach by O. Rosenbach in the expression "gastric insufficiency." The same idea had been suggested in the writings of Stokes concerning the functions of the heart.

The "sufficiency"—*i. e.*, capacity for work, or functional efficiency of an organ—depends upon the condition of that organ and the demands upon it. Therefore, sufficiency is a relative term only, and hence, if we find that an organ at a given examination shows insufficiency, we mean that it is incapable of doing the work it needs to do in the body.

The study of the functional value of the kidney is an important supplement to the study of the anatomic features of this organ in health and disease. If we can find and exactly measure the amount of work that the kidneys are doing, and if we can compare this amount of work with that of normal kidneys in a man of the same size, weight, and age, we gain a means of determining the actual value of a diseased kidney from a functional viewpoint. It is, of course, important to know what lesions are present in the kidneys; whether they are acute or chronic, parenchymatous or interstitial, but it is also of great value to know, both for prognosis and for the choice of treatment, the amount of functional efficiency left in a diseased kidney – *i. e.*, whether it is sufficient for the present needs of the body. The functional study of an organ, as Virchow pointed out long ago, broadens our knowledge of pathology and is just as important as the anatomic study of its lesions.

But, in addition to its general value in pathology, diagnosis, and prognosis, the functional state of the kidneys, or usually of one kidney as compared with the other, has become highly important of late in *surgical affections of these organs.* Just as one ventricle of the heart may compensate for the functional inefficiency of the other, so one kidney may compensate for the functional insufficiency of its fellow. When one kidney is perfectly healthy, the removal of the other, functionally useless kidney, which may be the seat of a suppurative condition, a malignant tumor, tuberculosis, etc., is not fraught with much danger to the patient's life, as the healthy kidney will take care of the work of both. On the other hand, should the opposite kidney be the seat of a chronic nephritis, showing itself in a more or less marked insufficiency, then nephrectomy is contraindicated. Modern surgery regards as unjustifiable any nephrectomy which has not been preceded by an examination of the comparative functional values of each kidney, the urine being drawn directly from each ureter by means of ureteral catheters introduced through a special cystoscope.

The data of ordinary uranalysis, etc., may give a clue to the anatomic conditions present or to the extent of the anatomic lesions, but do not give a ready means of calculating the actual amount of work a kidney can do. "For the fate of a patient does not depend upon the anatomical changes in the kidneys. It depends upon the interference with the function of this organ which is produced by these lesions" (Cooper). A kidney may be diseased, yet very nearly perfect in function, as enough healthy parenchyma may be left to do its work.

The special methods which have been devised for measuring the functional efficiency of the kidneys, or of each of these organs separately, are as follows:

1. By determining the molecular concentration of the urine—*i. e.*, the relative number of molecules in a given volume.
    - (*a*) By measuring freezing-point (cryoscopy).
    - (*b*) By measuring the electric conductivity of the urine.
2. By measuring the rate of excretion of urine in the kidneys:
    The methylene-blue test (Achard and Castaigne).
3. By measuring the chemic activity of the kidneys:
    The phloridzin test (Casper and Richter).

4. By measuring the relative amount of metabolic products retained in the blood, the freezing-point of the blood (cryoscopy) giving its molecular concentration (von Korányi).

1. DETERMINING THE FREEZING-POINT OF THE URINE.

Cryoscopy is the study of dissolved substances by observing the freezing-point of their solutions. The physical laws which underlie cryoscopy were discovered by Raoult in 1882, although they had been partly forecast and foretold by DeCoppet in 1872 and were supplemented by laws deduced from experimental researches by Van't Hoff in 1886. The application of cryoscopy to the study of urine, blood, and other body-fluids is due to von Korányi, of Budapest, who first introduced this method into clinical work in 1897.

It would be beyond our scope to enter into the intricacies of the physics of solutions upon which the freezing-point method is based. It will be enough if we say that *the freezing-point of a solution varies in proportion to the number of molecules of a substance in a given volume of the solvent.* The more concentrated the solution, the greater the number of molecules, the *lower* the freezing-point. This is simply a more exact statement of the well-known fact that a solution of salt in water freezes at a lower temperature than does water alone. The number of hundredths of a degree Centigrade at which freezing takes place below zero represents *the ratio* of the molecules dissolved in 1 c.c. of the solution. Thus, if urine may be found to freeze at

1.30°, it may be assumed that there are 130 molecules of solids in 1 c.c. of this urine. This figure is merely a conventional way of calculating, and we do not mean to state the *actual number* of molecules, which cannot be found, but merely to designate the ratio of molecules in this particular solution as compared to other solutions.

Cryoscopy is, therefore, based upon the principle established experimentally that *for every additional molecule of dissolved solids in a solution the freezing-point sinks to some extent and that, therefore,* by comparing the freezing-point of different solutions we can determine the ratio of molecular constitution.*

The technic of cryoscopy is by no means simple, on account of the delicacy of the observations, the variations in the freezing-point of urine being in hundredths of one degree Centigrade. A sample of the whole amount passed in twenty-four hours must be obtained, and 10 or 15 c.c. of this are sufficient for the cryoscopic test. The latter is performed in a special apparatus known as the *cryoscope*, of which there are a number of modifications, the original types being constructed by Raoult and by Beckmann. (See Fig. 75.) Essentially the apparatus consists of an extremely delicate thermometer* gradu-

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* There is, however, a very slight error in this calculation, which depends upon the fact that there is a difference between the freezing-point actually observed, and the calculated freezing-point, expressing the sinking of the point of congealing corresponding to the molecular constitution of a solution of known quantitative composition. This difference is very slight, does not amount to more than one-sixtieth of the figure obtained, and probably depends upon what is known as *dissociation.* In virtue of this phenomenon, which takes place to a greater or lesser extent in all solutions of salts, the molecules are split up or dissociated into their *ions* or radicles (such as *Na* and *Cl* in the case of *NaCl*). Each of the *ions* exerts the same influence upon the freezing-point as an *independent molecule*, and so the freezing-point is lowered more markedly than it should be from the actual number of molecules corresponding to the amount of the substance dissolved.

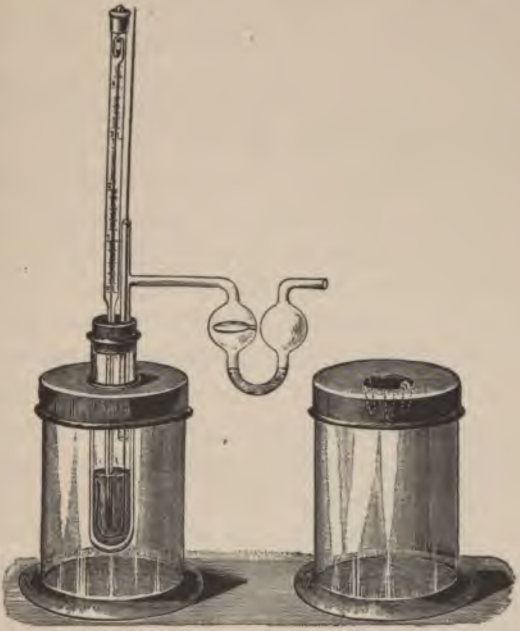

Fig. 75.—Beckmann's cryoscope.

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* The thermometer used in all cryoscopes was devised by Beckmann. The introduction of this instrument into chemic technic may be said to have marked an era in the history of physical chemistry. The Beckmann thermometer is unlike the ordinary instrument in that it has a reservoir of mercury at the top of the capillary, and by shaking the thermometer one can add to or sub-

ated to $\frac{1}{100}$ of a degree, the bulb of which dips into a test-tube filled with the urine. Outside of this is another test-tube containing alcohol or a solution of glycerin, so that the urine is inclosed in a double-walled chamber with one of these fluids in the interspace. The outer test-tube is surrounded by a mixture of ice and salt packed in a jar. A spiral of platinum wire or of hard rubber is arranged so that by means of it the urine can be constantly stirred around the thermometer, thus keeping the temperature of all parts of the sample uniform. The mercury begins to sink rapidly when the fluid approaches the freezing-point. It then rises and fluctuates for a time until it finally settles at a point below zero, which is read accurately as the freezing-point of the urine. Various mechanical improvements, such as automatic stirrers moved by clock-work, etc., have been devised, and in France the evaporation of ether or carbon disulphid is preferred by many to the use of ice for the purpose of freezing.

Clinical Applications of Cryoscopy.— The total number of molecules in a given urine is expressed by the freezing-point thereof, Δ. The normal freezing-point of urine ranges between —1.30° and —2.20° C. When there are lesions in the kidneys interfering with the functional activity of these organs, the freezing-

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tract from the length of the column of mercury. In this manner the thermometer may be "set" to read at any temperature. It is graduated so as to cover only a few degrees, thus giving a long scale which is subdivided into hundredths, and these, with the aid of a magnifying-glass, may be read to thousandths. Before using, the freezing-point of water should be determined with it, and any deviation from 0° C. should be noted as a correction.

point rises,—*i. e.*, approaches zero Centigrade,—because the total number of molecules excreted is diminished. A urine freezing at below —1° C. is usually considered as abnormal. In extremely severe cases of chronic nephritis, with uremia, the freezing-point is close to or actually at zero. The symbol Δ, by common consent, stands for the number of dissolved molecules in one cubic centimeter of urine, as expressed by the freezing-point in tenths and hundredths of a degree Centigrade. If V stands for the amount of urine eliminated in twenty-four hours, and P for the weight of the patient in kilograms, then the formula $\Delta \times \frac{V}{P}$ represents the total number of molecules eliminated in the urine per kilogram of body-weight in twenty-four hours. The comparison of the value of $\Delta \times \frac{V}{P}$ in different persons makes the freezing-point method more exact as a measure of functional activity than the mere comparison of the cryoscopic coëfficient, Δ, alone.

But not only is cryoscopy said to show the extent of the functional damage done by a lesion as a whole. By means of a simple calculation we can determine whether it is the tubular epithelium or the glomeruli that are most interfered with by the lesion, or whether only one of these classes of structures is affected while the other retains its normal functional activity.

In order to understand this application of cryoscopy we must go back to the theory of urinary secretion promulgated by von Korányi, which has already been dealt with in the introductory chapter of this book. The urine is separated from the blood by a membrane consisting of the glomerular structures (capsule, epithelium, and capillaries), and of the tubular epithelium. The glomeruli filter the water and the sodium chlorid into the tubules out of the blood, while the tubular epithelium excretes urea and other characteristic solids from the blood into the tubules, where the water, sodium chlorid, and urinary solids, such as urea, etc., all mingle to form the urine. The *urine is made up of two classes of molecules*—those of urea, etc., which are products of the body metabolism (*metabolic molecules*), and those of sodium chlorid, which are eliminated in the urine after having been taken in as such (*non-metabolic molecules*).

Now, if we subtract the number of molecules of sodium chlorid, as obtained by quantitative tests, from the total number of molecules Δ expressed by the freezing-point, we obtain the number of metabolic molecules δ, and the formula $\delta \cdot \frac{V}{P}$ then expresses the number of metabolic molecules per kilogram of body-weight eliminated in twenty-four hours, just as $\Delta \cdot \frac{V}{P}$ showed (see above) the total number of molecules contained in the urine of twenty-four hours per kilogram of body-weight. The ratio between the total number of molecules (Δ) and the number of metabolic molecules (δ) is expressed as follows: $\frac{\Delta}{\delta}$, and this value is really the leading factor in calculating the functional activity of the kidneys.

The presence of lesions in the glomeruli is followed by lessened filtration of chlorids into the sets of molecules reduced to their simplest terms. More elaborate formulæ have been devised, but they are often confusing. For all practical purposes the equations given will suffice, and the matter may be summed up by stating that $\Delta\frac{V}{P}$ is virtually a measure of the filtration work of the glomeruli, while $\frac{\Delta}{\delta}$ represents the excretion work of the tubular epithelia.

From these glimpses of the ingenious structure which has been built up from the data of cryoscopy the student must not conclude, however, that this method of functional urinary diagnosis is either well established or absolutely trustworthy. As yet there are too many conflicting results in clinical work with cryoscopy. At most, the method may be employed now as a corroborative test when other means of determining the functional value of the kidneys are also used for control purposes. There are still many difficulties to be overcome, and many questions to be solved about cryoscopy, before it can take a permanent place in the methods of urinary diagnosis. At present the whole matter is still in the experimental stage, and the student has here been made acquainted merely with the general principles of the method, in order that he may be able to follow its development in the future with understanding.*

* For further details concerning cryoscopy and its applications the reader is referred to Claude and Balthazard, "La Cryoscopie des Urines," Paris, Baillère et Fils, 1901; also to Casper and Richter, "Die functionelle Nierendiagnostik," Berlin, Urban and Schwarzenberg, 1901.

2. DETERMINING THE ELECTRIC CONDUCTIVITY OF THE URINE.

This method has been applied to urine with a view of measuring the molecular concentration of this complex solution. The process depends upon the fact that the electric conductivity of a solution —*i. e.*, its power to conduct or carry a current—varies with its molecular concentration.

The conductivity of a solution may be measured by Kohlrausch's method,* in which an alternating current is passed between platinum electrodes, through the solution whose conductivity it is desired to know. The resistance of the solution is balanced against a rheostat on a Wheatstone bridge, the point of equilibrium being determined by means of a telephone "receiver."

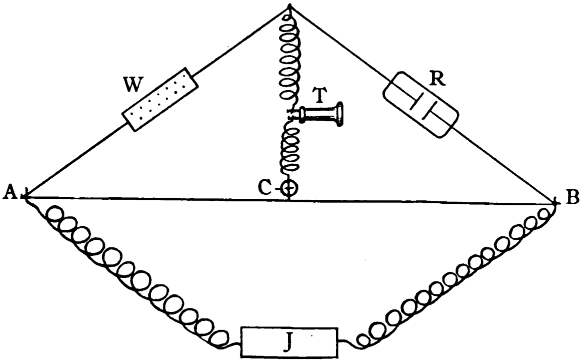

Fig. 76.—Kohlrausch's apparatus (Jones).

W is a rheostat or set of resistance coils. The meter-stick A B is divided into millimeters, and over it is stretched a wire of manganene (alloy of German silver and manganese); J is a small induction coil furnishing the alternating current; R is the glass cup for the solution, with platinum sheet electrodes. The telephone T is connected with the rheostat and the resistance vessel R, as well as with the bridge wire AB, by means of a slider. The point of equilibrium is ascertained by moving the slider along the wire until the sound of the coil is no longer audible in the telephone.

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* "Wied. Annalen," 1879, vol. vi, p. 145.

The conductivity of the urine in R is calculated from the position of the slider C on the scale, thus:

$AC = a$ r = resistance in rheostat.
$BC = b$ r_1 = resistance in vessel R.

Then $rb = r_1 a$; and $r_1 = \frac{rb}{a}$, and conductivity, c = the reciprocal of resistance, viz., $c = \frac{a}{rb}$.

The general law is that resistance increases with dilution—*i. e.*, conductivity decreases with dilution, but electric conductivity is affected by many factors which make the method difficult of clinical application and which create a series of exceptions to this rule. The method, on account of its complexity, has not gained general recognition as a means of diagnosis.*

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* For further details regarding electric conductivity of solutions the student is referred to the following works: H. C. Jones, "Elements of Physical Chemistry," New York, 1902; H. C. Jones, "Freezing Point, Boiling Point, and Conductivity Methods," Easton, Pa., 1902.

3. DETERMINATION OF THE RATE OF EXCRETION THROUGH THE KIDNEYS (METHYLENE-BLUE TEST).

This method of estimating the functional value of the kidneys was introduced by Achard and Castaigne.* It consists in injecting 0.05 gm. of methylene-blue in solution intramuscularly. The pigment appears in the urine in from one-quarter to one-half hour after this injection. If the excretion of the dye is delayed for one hour or longer, the kidneys are said to be diseased. Unfortunately, this test is not absolutely exact, as small amounts of healthy parenchyma, which are often present in extensively diseased organs, suffice for a prompt appearance of some methylene-blue in the urine after injection.

Recently Achard has perfected this method to a certain extent by introducing a quantitative estimation of the methylene-blue excreted. This is done by collecting the twenty-four hours' urine after the injection and comparing its color with that of a scale constructed by Achard, which assumes 25 mgm. of methylene-blue to be the normal amount excreted in twenty-four hours. In parenchymatous nephritis the method is of no value, according to Casper and Richter, who admit that it is useful in the interstitial form. Another objection to the value of this test is that some kidneys, or all kidneys even, may have a selective action upon methylene-blue, and while they excrete this dye readily, may not be capable of excreting the urinary constituents;

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* "Gazette des Hôpitaux," June 11, 1898.

or, vice versâ, that they may act normally with all other substances, but cannot excrete methylene-blue promptly.

4. DETERMINING THE CHEMIC ACTIVITY OF THE KIDNEY (PHLORIDZIN TEST).

An indication of the functional value of the kidneys may be gained through the study of its power of changing excreted substances chemically—a power inherent probably in the renal parenchyma.* An example of this chemic action of the kidneys is the appearance of sugar in the urine after the injection of a small dose of the glucosid phloridzin subcutaneously in healthy persons. In disease this chemic action is minimized or disappears completely. The absolute amount of glucose eliminated is, however, not a certain criterion of the functional state of the kidney. Casper and Richter have applied this method in conjunction with ureteral catheterization. They compare the functional activity of the two kidneys, basing their experiments on the fact that both kidneys in health excrete the same amount of sugar at the same stage of the phloridzin test.† The whole glycosuric attack lasts about three hours, and the urine is collected about one and one-half hours after injection.

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* Casper and Richter, "Berlin. klin. Wochenschr.," July 16, 1900, p. 643.

† Casper and Richter, " Die functionelle Nierendiagnostik," Berlin, 1901.

5. MEASURING THE RELATIVE AMOUNTS OF METABOLIC PRODUCTS RETAINED IN THE BLOOD (CRYOSCOPY OF THE BLOOD), COMPARING THIS WITH THE AMOUNT ELIMINATED IN THE URINE.

The description of this method properly belongs to text-books on the blood, but its importance in relation to renal functional diagnosis is such as to warrant mention here. Casper and Richter* consider it as the most rational method of determining the functional value of the kidneys. The chief advocate of this procedure is von Korányi, to whom we owe the application of cryoscopy to the urine. The method consists of measuring the freezing-point of the blood and that of the urine in the same person, the two fluids being obtained on the same day. This method has, however, certain limitations in practical application, and has not yet been very completely worked out. It is possible that it may prove of great value in the diagnosis of surgical renal affections.

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* *Loc. cit.*

CHAPTER XXIV.

PTOMAINS AND LEUKOMAINS.—TOXICITY OF URINE.

PTOMAINS.

Ptomains are complex organic substances, basic in character, resembling alkaloids in many respects, and formed by the action of bacteria upon nitrogenous matter, which may be either animal or vegetable in origin. Some ptomains are highly poisonous and are styled toxins (Brieger), while others are harmless.

According to Bouchard, Pouchet, and others, ptomains occur in normal urine and are increased in quantity in disease (Bouchard, Lépine and Guerin, etc.). Villiers found a constant increase of these substances in measles, diphtheria, and pneumonia. Pouchet found them in cholera; Feltz in cancer; Lépine in pneumonia, and Griffiths and Albu have isolated a series of ptomains in a great variety of diseases. Baumann and von Udránszky showed the presence of two ptomains, first described by Brieger—putrescin ($C_4H_{12}N_2$) and cadaverin ($C_5H_{14}N_2$)—in the urine in a case of cystinuria and cystitis.

LEUKOMAINS.

Leukomains are basic substances found in living tissues, which do not result from the action of bacteria, but are the product of fermentation or of retrograde changes in the organism. While leukomains are the products of normal life-processes, ptomains are the results of putrefaction.

Leukomains in the urine are divided into two groups—the uric-acid group and the creatinin group. The uric-acid group includes bases related to uric acid—viz., adenin, hypoxanthin, guanin, xanthin, heteroxanthin, etc., carnin, episarkin, pseudoxanthin, etc. The creatinin group, according to Gautier, includes creatinin, creatin, crusocreatin, xanthocreatin, amphicreatin, and two unnamed bases.

Brieger and von Udránszky, and Baumann and Stadthagen* deny the occurrence of ptomains and leukomains in normal urine, and present very strong objections to Bouchard's teachings.

The clinical interest in the presence of ptomains and leukomains in the urine lies in the fact that these substances are the chemic bases of infectious diseases, and that possibly specific substances may be isolated from the urine in various maladies. The subject, however, has not yet been sufficiently well worked out to bear direct application in clinical work.†

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* Quoted by Hammarsten, "Physiological Chemistry" (Mandel), third edition, New York, 1901, p. 463.

† For details regarding the chemistry of ptomains and leukomains see Vaughan and Novy, "Cellular Toxins," Philadelphia, 1902. For a bibliography of ptomains and leukomains in the urine see Neubauer and Vogel, "Analyse des Harnes" (Huppert), Wiesbaden, 1898.

TOXICITY OF URINE.

It has been known for a long time that suppression of urine is followed by systemic poisoning of a definite type. In 1881 Feltz and Ritter showed that normal urine was poisonous by injecting it into animals and finding that a certain dose of urine was fatal. Later, Bouchard investigated the poisonous properties of normal urine more thoroughly. In order to be able to compare the toxicity of urine under various conditions, Bouchard established what is known as the *urotoxic coëfficient*, which is the weight of rabbit in kilos that is killed by the quantity of urine excreted by one kilo of the person experimented upon in twenty-four hours.

The toxic symptoms produced by the intravenous injection of normal urine include contraction of the pupil, which dilates just before death, somnolence, coma, marked polyuria, frequent micturition, a lowering of the temperature, diminished reflexes of the conjunctiva and cornea, and death in coma or convulsions.

The toxicity of the urine, according to Bouchard, is greater during the day than at night. The day urine is strongly narcotic and but feebly convulsive, while the night urine is the reverse. The toxicity is diminished by active exercise in the open air. Bouchard found that in acute uremia the urine becomes non-toxic. He concludes that the urine's toxic properties are due to a number of substances which he could not isolate completely, but is not due to urea, uric acid, creatinin, etc., since these are non-toxic in large doses when injected into the blood.

Some observers—*e. g.*, Stadthagen, Beck, and v. d. Bergh*—deny that any specific poisonous substance occurs in normal urine. They claim that the poisonous action of the urine is due partly to the potassium salts and partly to the other normal constituents—urea, creatinin, etc.—which have very little toxic effect individually.

In disease the toxic power of the urine may be either increased or diminished. It is generally increased in acute infectious diseases and fevers, provided the kidneys remain healthy. The toxic powers of the urine become more or less diminished according to the extent of the damage done to the kidneys, and in extensive renal lesions the urine may become almost non-toxic. In uremia the kidneys no longer eliminate the poisons from the system, and the urine is non-toxic. The toxicity of the urine is considerably raised in most diseases, however—*e. g.*, in tetanus (Labbé), in cholera (Bouchard), in septicemia (Feltz), in diphtheria (Roux and Yersin), etc.

Bouchard has shown that from 30 to 60 c.c. of normal urine injected intravenously will kill a rabbit weighing one kilogram. A man weighing 60 kilos and passing 1200 c.c. of urine daily secretes enough poison to kill 24 kilos of animal, if 50 c.c. are necessary to kill one kilo of living matter. This standard is used in determining the relative value of the "urotoxic coëfficient" referred to above.

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* Quoted by Hammarsten, *loc. cit.*

APPENDIX.

ROUTINE OF EXAMINATION.* REAGENTS, APPARATUS, ETC.

While a complete urine examination, as may be seen from the foregoing pages, calls for a great deal of time and labor and a full mastery of technical detail, routine analyses which are sufficient for every-day purposes require but a few minutes' time and are accomplished with comparatively simple means and with the fewest possible manipulations. In the following summary I mean to give the student, the busy physician, and the medical examiner for life insurance a few hints as to the best means of shortening the time and lessening the labor of urine analysis, without unduly interfering with the trustworthiness or accuracy of the results. Every one who has a large number of uranalyses to perform daily, or who has but a few minutes to devote to the examination of urine, will do well if he begins by devising a certain routine of work. Such routine examinations should be as rapid as is compatible with thoroughness and accuracy; they should include everything that is necessary for a clinical diagnosis, and exclude everything that is unnecessary or of purely theoretic interest. A routine of work may, indeed, be so devised that even unnecessary movements are saved, wherever possible, by simplifying the methods and arranging the order of the tests. Such moments, wasted in unnecessary trifling with minor details, are well saved and well invested in a longer time allotted to the study of the urine under the microscope.

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* *Cf.* Saxe, "Points on Technique in Routine Examinations of Urine," "Medical Examiner and Practitioner," Feb., 1904, p. 79.

Selection of Methods.—The first thing to be done when contemplating the analysis of a number of specimens is to determine, once for all, the methods that are to be used, and then to adhere to these methods unless forced to deviate from them by some special circumstance. This does not, of course, mean to exclude experimenting with various methods or modifications at our leisure.

It is the beginner who is usually undecided as to what method he shall use for a certain test, etc. The experienced man, as a rule, works with one method, or at the most with two, for the same part of the analysis.

As I have said in speaking of albumin tests, in practical work the best way is to use one test, with possibly a confirmatory test in reserve in case of doubt. This principle holds good in all parts of urine analysis. Select, therefore, the best method you know of—one that has proved efficient and practical in the hands of a large number of men—and stick to this method in your routine work. This has the obvious advantage that the man who works with one method will in a short time know all the vagaries, irregularities, possibilities, impossibilities, and sources of error in the one method which he uses.

The next rule to be observed in routine work is: In employing a given method, invariably use the same amounts of reagents, the same dilution, the same order, heating, if needed, for the same length of time—in short, using exactly the same manipulations for the same test in each analysis. This will enable a careful worker, after a time, to estimate with fair accuracy the quantity of a constituent from the bulk of a sediment or precipitate. Of course, such adherence to routine in details can be profitable only after one knows with perfect accuracy just how to perform a test to the best advantage with whatever materials (test-tubes, etc.) one may have on hand.

Routine of Work.—Necessarily each man must be a law unto himself in devising this routine, according to his tastes, the time at his disposal, and the requirements of his cases. The following order of examination is suggested as one that is apt to meet the average requirements. The tests selected are those which have proved trustworthy in my own work and which have been found satisfactory by a large number of observers:

ROUTINE OF EXAMINATION.

1. **Physical Examination.**—The urine is poured into a small cylinder and a urinometer is immersed in it, together with a strip of blue litmus-paper. While the urinometer is allowed to settle in position, the *color* of the urine is determined by a comparison

with Vogel's scale, which hangs directly opposite on a wall. The same glance tells us its *transparency*, the presence of a *sediment*, and, before the specific gravity is read, the *odor* is ascertained. These characteristics are noted on the record-blank (see p. 372), and then the urinometer scale is read. A portion of the urine is now poured into a small filter, the consistence of the fluid being noted as this is done, and the filtered urine is used for many of the subsequent tests, a constant supply of it being kept up by filling the filter from time to time.

2. **Chemic Examination.**—This should begin with the estimation of urea by Doremus' method, because while the nitrogen gas is forming we can attend to the other tests and then read the scale of the apparatus. The reagent is mixed, preferably by using Rice's solutions (see p. 126), but if pure bromin be employed for Knop's original method, a glass tray should be provided on which are placed —(1) A bottle of bromin; (2) a glass-stoppered bottle holding just enough soda solution to fill the Doremus tube; (3) a 1-c.c. pipet with nipple-end, and (4) a bottle of ammonia water. The tray is placed outside a window, preferably on the side of the house away from the wind, and 1 c.c. of bromin should be carefully measured in the pipet and dropped into the soda solution with the least possible loss of bromin fumes. If a drop of bromin falls upon the tray, it should be quickly covered with a few drops of ammonia, and a whiff of the latter may be taken to counteract the irritant action of the fumes.

Albumin.—While the urea test is under way we proceed to look for albumin. For this purpose I generally employ first Heller's test with pure cold nitric acid, and, as a confirmatory test, Robert's method with the horismascope or the ferrocyanid test. The latter tests may be used first if very small amounts of albumin are expected. If albumin is found, Esbach's quantitative method is applied, the tube being allowed to stand until the following day.

Sugar.—While the test-tube of the albumin test is allowed to stand for a few moments to show the full development of the ring, we mix and dilute the Fehling's solution and bring it to a boil. The urine is added, and if a positive reaction is obtained, we at once set up the Einhorn saccharometer with yeast and urine and allow it to stand for twenty-four hours.

Indican is the next substance looked for. Here I am in the habit, in routine work, of employing Heller's very simple and efficient method. I believe that this test is not used so widely as it should be in this country. The same amount of urine and of the acids is always used, and a fair estimate is obtained of the amount of indican in the urine.

Bile.—In testing for bile we may use the filter-paper, which has become in the meanwhile well saturated with the filtering urine. While the indican test is allowed to reach its completion, a drop of pure nitric acid is placed on the filter, producing a green spot which changes to red if an excess of bile is present. Often this test is not necessary, as in Heller's test for albumin an excess of

BLANK FOR URINE EXAMINATION.

Name . . . . Received . . . .

Dr. . . . . Examined . . . .

EXAMINATION OF URINE.

Passed . . . . spontaneously; by catheter . . . .
Obtained from the . . . . . . kidney by ureteral catheterization by . . . .
Volume in twenty-four hours . . . . c.c. . . . . ounces.

PHYSICAL EXAMINATION.

1. Color, No. . . . . . . Vogel's scale.
2. Odor . . . .
3. Consistence . . . .
4. Transparency . . . .
5. Sediment . . . .
6. Specific gravity . . . . . at 15° C.
7. Total solids . . . . . . gm. in liter.
8. Cryoscopy . . . .

CHEMIC EXAMINATION.

1. Reaction . . . .
2. Acidity . . . .
3. Albumin: Heller's . . . .
   Robert's . . . .
   Ferrocyanid . . . . . .
   Amount: Esbach's . . gm. in liter
4. Other Proteids . . . .
   Nucleo-albumin . . . .
   Mucin . . . .
   Peptone . . . .
   Globulin . . . .
5. Glucose: Fehling's . . . .
   Phenylhydrazin . . . .
   Fermentation . . . . %
6. Urea . . . . . . %; . . gm. in liter.
7. Uric acid . . . .
8. Purin bodies . . . .
9. Chlorids . . . .
10. Phosphates, earthy . . . .
11. Phosphates, alkaline . . . .
12. Sulphates . . . .
13. Diacetic acid . . . .
14. Acetone . . . .
15. Bile . . . .
16. Indican . . . .
17. Blood . . . .
18. Diazo-reaction . . . .
19. Other chemic elements . . . . . .
    . . . .
    . . . .

MICROSCOPIC EXAMINATION.

1. Crystals: Uric Acid . . . .
   . . . .
   Triple phosphate . . . .
   Calcium oxalate . . . .
   Other forms . . . . . .
   . . . .
2. Amorphous sediment:
   Urates . . . .
   Phosphates . . . .
   Other forms . . . . . .
   . . . .
3. Mucus: . . . .
4. Pus . . . .
   . . . .
5. Epithelium . . . .
   from . . . .
   . . . .
6. Blood . . . .
7. Cylindroids . . . .
8. Casts: Hyaline . . . .
   Granular . . . .
   Epithelial . . . .
   Blood . . . .
   Waxy . . . .
   Mixed . . . .
9. Micro-organisms . . . .
10. Other elements . . . .
    . . . .

Remarks: . . . .

. . . .

. . . . M. D.

LIST OF REAGENTS, APPARATUS, ETC.

Reagent bottles of appropriate sizes (250 c.c. for liquids and 125 c.c. for solids) are made by firms supplying chemic apparatus, and should be made of glass free from lead and other impurities. The bottles should be fitted with glass stoppers, and those for solutions of salts, such as sodium hydrate, etc., should have stoppers coated with a mixture of paraffin and vaselin.

All reagents should be purchased chemically pure, unless otherwise specified. All standard solutions for chemic analysis are described by the United States Pharmacopœia, and should conform to its standard, unless otherwise mentioned in the text of this book.

The reagents marked with an asterisk in the following list are essential for routine work according to the foregoing scheme. The other substances include the principal reagents used in urine examinations of more elaborate character:

LIQUID REAGENTS.

Distilled water (H_2O).
Acid, Acetic (c. p.), U. S. P. ($HC_2H_3O_2$).
Acid, Acetic, Glacial, U. S. P.
Acid, Boric (c. p.) (H_3BO_3), sat. sol.
* Acid, Hydrochloric (c. p.) (HCl).
Acid, Hydrochloric, Commercial (for cleaning glassware).
* Acid, Nitric (c. p.) (HNO_3).
Acid, Nitric (brown, fuming; nitrosonitric).
Acid, Picric ($C_6H_2(NO_2)_3OH$), 8 gr. to 1 oz. = sat. sol.
Acids, Picric and Citric (Esbach's solution, see p. 70).
Acid, Salicylsulphonic, sat. sol.
Acid, Sulphuric (c. p.) (H_2SO_4).

* Ammonium Hydrate, U. S. P. (NH_4OH).
Ammonium Chlorid, sat. sol.
Ammonium Sulphate, sat. sol.
Sodium Hydrate, U. S. P. ($NaOH$).
* Sodium Hydrate for Urea (Knop's).
* Sodium Hydrate for Urea (Rice's).
Sodium Chlorid ($NaCl$), sat. sol.
Sodium Nitroprussid [$NaFe(NO)(CN)_5 + 2H_2O$], sat. sol.
Potassium Hydrate, U. S. P. (KOH).
* Potassium Ferrocyanid ($K_4Fe(CN)_6$), 1 : 20.
Potassiomercuric Iodid (Tanret's, see p. 62).
* Potassium and Sodium Tartrate (Fehling's, see p. 93).
* Magnesium Fluid (see p. 201).
Magnesium Sulphate and Nitric Acid (Robert's, see p. 65).
Barium Chlorid ($BaCl_2$, 4 oz.; H_2O, 16 oz.; HCl, 1 oz.).
* Copper Sulphate (Fehling's, see p. 93).
* Silver Nitrate ($AgNO_3$), 1 : 8.
Iron Chlorid (Fe_2Cl_6), 1 : 10.
Lead Acetate ($PbO_2 [C_2H_3O]_2$), 1 : 4.
Lead Acetate, Basic ($Pb_2C_2H_3O_2 \, 2PbO$) 1 : 4.
Mercuric Chlorid (Spiegler's, see p. 64).
Mercuric Nitrate (Millon's, see p. 88).
Hydrogen Peroxid (H_2O_2), U. S. P.
* Bromin (c. p.) (Br).
* Bromin (Rice's solution, see p. 126).
Tincture Iodin, U. S. P.
Tincture Guaiac, U. S. P., fresh.
Turpentine.
Alcohol.
Chloroform.
Ether.
* Formalin, 40 per cent.

Also the following standard volumetric solutions:

Decinormal Potassium Hydrate.
Decinormal Sodium Hydrate.
Decinormal Silver Nitrate. }
Decinormal Potassium Bichromate ($K_2Cr_2O_7$). } For chlorids.
Standard Uranium Nitrate. }
Standard Sodium Acetate. } For phosphoric acid.
Potassium Ferrocyanid.
Standard Barium Chlorid. }
Potassium Sulphate (K_2SO_4), 20 per cent. } For sulphates.

SOLID REAGENTS.

* Acid, Picric.
* Acid, Citric.
Ammonium Sulphate.
Ammonium Chlorid.
Sodium Hydrate.
Sodium Chlorid.
Sodium Acetate.
Sodium Nitrite.
Sodium Carbonate.
Sodium Nitroprussid.
Potassium Hydrate.
Potassium Iodid.
Potassium Chromate.
Potassium Ferrocyanid.
Potassium Chlorate.
* Magnesium Sulphate.
Copper Sulphate.
Lead Acetate.
Mercuric Chlorid.
* Phenylhydrazin.
* Yeast.
* Litmus-paper.

BACTERIAL STAINS, ETC.

1. Methylene blue, sat. sol. in 95 % alcohol (1 part in 9 of water for staining bacteria).
2. Gentian violet, sat. alcoholic sol. (of this, 16 c.c. mixed with 84 c.c. of aniline water, for Gram's stain).
3. Gram's solution (iodin, 1; potassium iodid, 2; water, 300).
4. Bismarck brown, sat. aqueous sol.
5. Aniline water (aniline oil, 5; water, 95; shake and filter).
6. Carbol-Fuchsin (Ziehl-Neelson's) (Fuchsin, sat. alcoholic sol., 10; carbolic-acid water, 5 %, —90).
7. Nitric acid, 20 %
8. Alcohol, 70 %.

APPARATUS.

Test-tubes, 2 or 3 dozen, assorted sizes.
Pipets, plain glass, ½ dozen.
Pipets, graduated, 5, 10, 25 and 50 c.c.
Glass rods, 8 inches long each.
Beakers, thin glass, with lip, nest of 6.
Florence flasks, 250 c.c.. 500 c.c.
Watch-glasses, nest of 6.
Porcelain evaporating dishes, nest of 6.
Conic glasses, 4.
Wine-glasses, 2.
Ground-glass covers, square.
Cylinders for urinometer, 4 ounces, and for urine, 12 ounces.
Wash-bottle.
Funnels, glass, 3 assorted sizes.
Droppers, nipple.
Graduates, for 100, 500, and 1000 c.c., marked also in ounces.
Graduate, for 15 c.c., marked also in minims.
Urinometer (Squibb's, etc.).
Urinopyknometer (see p. 43).
Saccharometer, Einhorn's.
Doremus' urea apparatus; or Hinds'.
Esbach's albuminometer.
Horismascope (albumoscope).
Uricometer, Ruhemann's.
Purin apparatus, Camerer's
Thermometer, Centigrad
Burets, 50 c.c. each, grad

Balance, accurate, with weights.
Test-tube rack.
Test-tube brushes, sponge end.
Filter-paper, round, assorted sizes, white " c. p." quality.
Water-bath, copper, fitted with rings.
Filter and buret stand, metal with solid base.
Wire gauze, several squares 4 by 4 inches each.
Tripod and triangle for heating.
Bunsen burner and tubing; or
Alcohol lamp.
Test-tube holder, wood or wire.
Platinum foil.
Platinum wire in glass-rod handle.
Centrifuge (see page 218).
Slides and cover-glasses.
Microscope (see page 222).

THERMOMETRIC EQUIVALENTS.

Cent.	Fahr.	Cent.	Fahr.	Cent.	Fahr.
110°	230°	41°	105.8°	31°	87.8°
100	212	40.5	104.9	30	86
95	203	40	104.0	25	77
90	194	39.5	103.1	20	68
85	185	39	102.2	15	59
80	176	38.5	101.3	10	50
75	167	38	100.4	+5	41
70	158	37.5	99.5	0	32
65	149	37	98.6	—5	23
60	140	36.5	97.7	—10	14
55	131	36	96.8	—15	+5
50	122	35.5	95.9	—17.8	0
45	113	35	95.0	—20	—4
44	111.2	34	93.2	0.54° =	1°
43	109.4	33	91.4	1 =	1.8
42	107.6	32	89.6	2 =	3.6

RELATIONS OF ENGLISH TO METRIC SYSTEMS.

1 grain = 64.8 milligrams.
1 ounce = 28.3 grams.
1 pound = 453.6 grams.
1 gram = 15.432 grains.
1 kilo = 2 pounds 3 ounces.
1 minim = 0.059 cubic centimeter.
1 fluidram = 3.5 cubic centimeters.
1 fluidounce = 28.39 cubic centimeters.
1 pint = 567.9 cubic centimeters.
1 c.c. = 16.9 minims.
1 liter = 35.2 fluidounces.
1 inch = 2.54 centimeters.
1 foot = 30.48 centimeters.
1 yard = 91.44 centimeters.
1 centimeter = 0.39 inch.
1 meter = 39.37 inches.

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